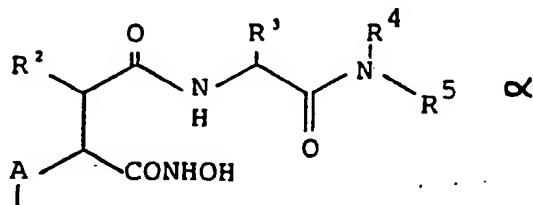
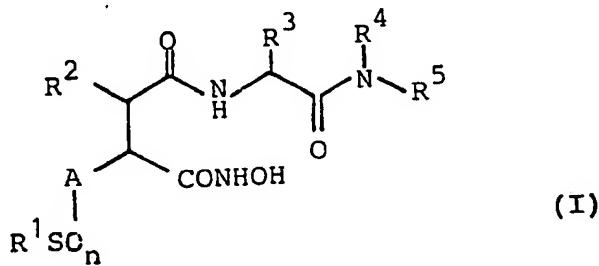




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(54) Title: HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS



(57) Abstract

Compounds of general formula (I), wherein R¹ represents hydrogen or an alkyl, phenyl, thiophenyl, substituted phenyl, phenylalkyl, heterocycl, alkylcarbonyl phenacyl or substituted phenacyl group; or, when n = 0, R¹ represents SR^X, wherein RX represents a group (α); R² represents a hydrogen atom or an alkyl, alkenyl, phenylalkyl, cycloalkylalkyl or cycloalkylalkyl group; R³ represents an amino acid residue with R or S stereochemistry or an alkyl, benzyl, (C₁-C₆ alkoxy) benzyl or benzyloxy(C₁-C₆ alkyl) group; R⁴ represents a hydrogen atom or an alkyl group; R⁵ represents a hydrogen atom or a methyl group; n is an integer having the value 0, 1 or 2; and A represents a hydrocarbon chain optionally substituted with one or more alkyl, phenyl or substituted phenyl groups; and their salts and N-oxides are collagenase inhibitors and are useful in the management of disease involving tissue degradation and/or the promotion of wound healing. Diseases involving tissue degradation include arthropathy (particularly rheumatoid arthritis), inflammation, dermatological diseases, bone resorption diseases and tumour invasion.

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1 HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS.

2

3 This invention relates to pharmaceutically and
4 veterinarily active compounds, which are derivatives of
5 hydroxamic acid.

6

7 The compounds of the present invention act as
8 inhibitors of metalloproteases involved in tissue
9 degradation, such as collagenase, which initiates
10 collagen breakdown, stromelysin (proteoglycanase),
11 gelatinase and collagenase (IV). There is evidence
12 implicating collagenase as one of the key enzymes in
13 the breakdown of articular cartilage and bone in
14 rheumatoid arthritis (Arthritis and Rheumatism, 20,
15 1231 - 1239, 1977). Potent inhibitors of collagenase
16 and other metalloproteases involved in tissue
17 degradation are useful in the treatment of rheumatoid
18 arthritis and related diseases in which collagenolytic
19 activity is important. Inhibitors of metalloproteases
20 of this type can therefore be used in treating or
21 preventing conditions which involve tissue breakdown;
22 they are therefore useful in the treatment of
23 arthropathy, dermatological conditions, bone
24 resorption, inflammatory diseases and tumour invasion
25 and in the promotion of wound healing. Specifically,
26 compounds of the present invention may be useful in the
27 treatment of osteopenias such as osteoporosis,
28 rheumatoid arthritis, osteoarthritis, periodontitis,
29 gingivitis, corneal ulceration and tumour invasion.

30

31 A number of small peptide like compounds which
32 inhibit metalloproteases have been described. Perhaps
33 the most notable of these are those relating to the

1 angiotensin converting enzyme (ACE) where such
2 agents act to block the conversion of the decapeptide
3 angiotensin I to angiotensin II a potent pressor
4 substance. Compounds of this type are described in
5 EP-A-0012401.

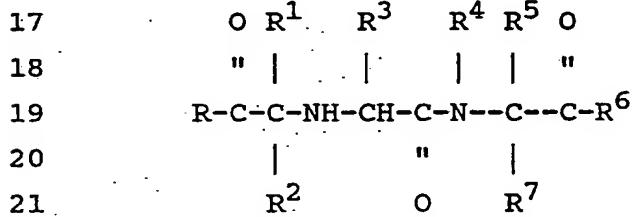
6

7 Certain hydroxamic acids have been suggested as
8 collagenase inhibitors as in US-A-4599361 and
9 EP-A-0236872. Other hydroxamic acids have been prepared
10 as ACE inhibitors, for example in US-A-4105789, while
11 still others have been described as enkephalinase
12 inhibitors as in US-A-4496540.

13

14 EP-A-0012401 discloses antihypertensive compounds of
15 the formula:

16



22

23 wherein

24

25 R and R⁶ are the same or different and are hydroxy,
26 alkoxy, alkenoxy, dialkylamino alkoxy, acylamino
27 alkoxy, acyloxy alkoxy, aryloxy, alkyloxy, substituted
28 aryloxy or substituted aralkoxy wherein the substituent
29 is methyl, halo, or methoxy, amino, alkylamino,
30 dialkylamino, aralkylamino or hydroxyamino;

31

32

33

1 R¹ is hydrogen, alkyl of from 1 to 20 carbon atoms,
2 including branched, cyclic and unsaturated alkyl
3 groups;

4

5 substituted alkyl wherein the substituent is halo,
6 hydroxy, alkoxy, aryloxy amino, alkylamino,
7 dialkylamino, acrylamino, arylamino, guanidino,
8 imidazolyl, indolyl, mercapto, alkylthio, arylthio,
9 carboxy, carboxamido, carbalkoxy, phenyl, substituted
10 phenyl wherein the substituent is alkyl, alkoxy or
11 halo; aralkyl or heteroaralkyl, aralkenyl or
12 heteroaralkenyl, substituted aralkyl, substituted
13 heteroaralkyl, substituted aralkenyl or substituted
14 heteroaralkenyl, wherein the substituent is halor or
15 dihalo, alkyl, hydroxy, alkoxy, amino, aminomethyl,
16 acrylamino, dialkylamino, alkylamino, carboxyl,
17 haloalkyl, cyano or sulphonamido, aralkyl or
18 heteroaralkyl substituted on the alkyl portion by
19 amino or acylamino;

20

21 R² and R⁷ are hydrogen or alkyl;

22

23 R³ is hydrogen, alkyl, phenylalkyl,
24 aminomethylphenylalkyl, hydroxyphenylalkyl,
25 hydroxyalkyl, acetylaminoalkyl, acylaminoalkyl,
26 acylaminoalkyl aminoalkyl, dimethylaminoalkyl,
27 haloalkyl, guanidinoalkyl, imidazolylalkyl,
28 indolylalkyl, mercaptoalkyl and alkylthioalkyl;

29

30 R⁴ is hydrogen or alkyl;

31

32

33

1 R⁵ is hydrogen, alkyl, phenyl, phenylalkyl,
2 hydroxyphenylalkyl, hydroxyalkyl, aminoalkyl,
3 guanidinoalkyl, imidazolylalkyl, indolylalkyl,
4 mercaptoalkyl or alkylthioalkyl;

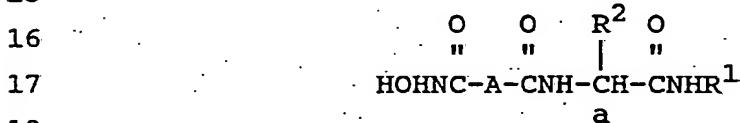
5

6 R⁴ and R⁵ may be connected together to form an alkylene
7 bridge of from 2 to 4 carbon atoms, an alkylene bridge
8 of from 2 to 3 carbon atoms and one sulphur atom, an
9 alkylene bridge of from 3 to 4 carbon atoms containing
10 a double bond or an alkylene bridge as above,
11 substituted with hydroxy, alkoxy or alkyl and the
12 pharmaceutically acceptable salts thereof.

13

14 US-A-4599361 discloses compounds of the formula:

15



19

wherein

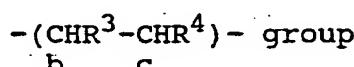
20 R¹ is C₁-C₆ alkyl;

21 R² is C₁-C₆ alkyl, benzyl, benzyloxybenzyl, (C₁-C₆
22 alkoxy)benzyl or benzyloxy(C₁-C₆ alkyl);

23 a is a chiral centre with optional R or S
24 stereochemistry;

25 A is a

26



29 or a -(CR³=CR⁴)- group wherein b and c are chiral
30 centres with optional R or S stereochemistry;

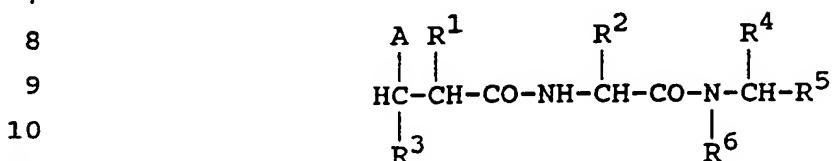
31

32

33

1 R^3 is hydrogen, C_1-C_6 alkyl, phenyl or phenyl(C_1-C_6
2 alkyl) and R^4 is hydrogen, C_1-C_6 alkyl, phenyl(C_1-C_6
3 alkyl), cycloalkyl or cycloalkyl(C_1-C_6 alkyl).

4
5 EP-A-0236872 discloses generically compounds of the
6 formula



13 wherein

15 A represents a group of the formula $\text{HN}(\text{OH})\text{-CO-}$ or
16 $\text{HCO-N}(\text{OH})\text{-:}$

18 R¹ represents a C₂-C₅ alkyl group;

20 R² represents the characterising group of a natural
21 alpha-amino acid in which the functional group can be
22 protected, amino groups may be acylated and carboxyl
23 groups can be amidated, with the proviso that R² can
24 not represent hydrogen or a methyl group;

26 R³ represents hydrogen or an amino, hydroxy, mercapto,
 27 C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ acylamino,
 28 C₁-C₆-alkylthio, aryl-(C₁-C₆ alkyl)-,
 29 amino-(C₁-C₆-alkyl)-, hydroxy(C₁-C₆-alkyl)-,
 30 mercapto(C₁-C₆ alkyl) or carboxy(C₁-C₆ alkyl) group,

1 wherein the amino, hydroxy, mercapto or carboxyl groups
2 can be protected and the amino groups may be acylated
3 or the carboxyl groups may be amidated;

4

5 R^4 represents hydrogen or a methyl group;

6

7 R^5 represents hydrogen or a C_1-C_6 acyl, C_1-C_6 alkoxy-
8 C_1-C_6 alkyl, di(C_1-C_6 -alkoxy)methylene, carboxy, (C_1-C_6
9 alkyl)carbiny, (C_1-C_6 alkoxy)carbiny, arylmethoxy
10 carbiny, (C_1-C_6 alkyl)amino carbiny or arylamino
11 carbiny group; and

12

13 R^6 represents hydroxy or a methylene group; or

14

15 R^2 and R^4 together represent a group- $(CH_2)_n-$, wherein n
16 represents a number from 4 to 11; or

17

18 R^4 and R^5 together represent a trimethylene group;

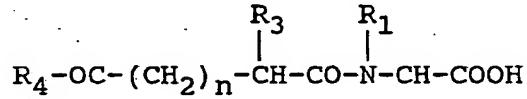
19

20 and pharmaceutically acceptable salts of such
21 compounds, which are acid or basic.

22

23 US-A-4105789 generically discloses compounds which have
24 the general formula

25



29 and salts thereof, wherein

30

31 R_1 is hydrogen, lower alkyl, phenyl lower alkylene,
32 hydroxy-lower alkylene, hydroxyphenyl lower
33 alkylene, amino-lower alkylene, guanidine lower

1 alkylene, mercapto-lower alkylene, lower
2 alkyl-mercапto-lower alkylene, imidazolyl lower
3 alkylene, indolyl-lower alkylene or carbamoyl
4 lower alkylene;
5 R_2 is hydrogen or lower alkyl;
6 R_3 is lower alkyl or phenyl lower alkylene;
7 R_4 is hydroxy, lower alkoxy or hydroxyamino; and
8 n is 1 or 2.

9
10 US-A-4496540 discloses compounds of the general
11 formula:

12
13 A-B-NHOH
14

15 wherein A is one of the aromatic group-containing amino
16 acid residues L-tryptophyl, D-tryptophyl, L-tyrosyl,
17 D-tyrosyl, L-phenylalanyl, or D-phenylalanyl, and B is
18 one of the amino acids glycine, L-alanine, D-alanine,
19 L-leucine, D-leucine, L-isoleucine, or D-isoleucine;
20 and pharmaceutically acceptable salts thereof.

21
22 It would however be desirable to improve on the
23 solubility of known collagenase inhibitors and/or
24 stomelysin inhibitors (whether as the free base or the
25 salt) and, furthermore, increases in activity have also
26 been sought. It is not a simple matter, however, to
27 predict what variations in known compounds would be
28 desirable to increase or even retain activity; certain
29 modifications of known hydroxamic acid derivatives have
30 been found to lead to loss of activity.

31
32 According to a first aspect of the invention, there is
33 provided a compound of general formula I:

1

2

3

4

5

6

7

8 wherein:

9

10 R^1 represents a C_1-C_6 alkyl, phenyl, thiophenyl,
 11 substituted phenyl, phenyl(C_1-C_6)alkyl,
 12 heterocyclyl, (C_1-C_6)alkylcarbonyl, phenacyl or
 13 substituted phenacyl group; or, when $n = 0$, R^1
 14 represents SR^X , wherein R^X represents a group:

15

16

17

18

19

20

21

22 R^2 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6
 23 alkenyl, phenyl(C_1-C_6)alkyl,
 24 cycloalkyl(C_1-C_6)alkyl or cycloalkenyl(C_1-C_6)alkyl
 25 group;

26

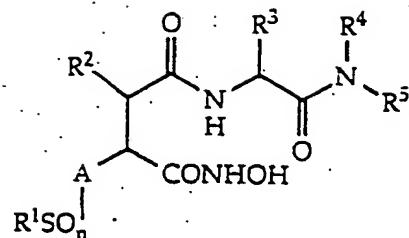
27 R^3 represents an amino acid side chain or a C_1-C_6
 28 alkyl, benzyl, (C_1-C_6 alkoxy)benzyl,
 29 benzyloxy(C_1-C_6 alkyl) or benzyloxybenzyl group;

30

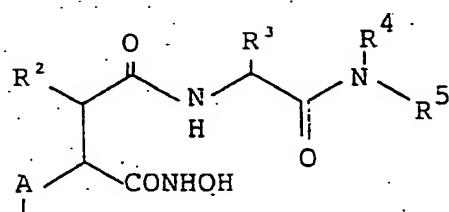
31 R^4 represents a hydrogen atom or a C_1-C_6 alkyl group;

32

33 R^5 represents a hydrogen atom or a methyl group;



(I)



1 n is an integer having the value 0, 1 or 2; and
2
3 A represents a C₁-C₆ hydrocarbon chain, optionally
4 substituted with one or more C₁-C₆ alkyl, phenyl
5 or substituted phenyl groups;
6
7 or a salt thereof.

8
9 Hereafter in this specification, the term "compound"
10 includes "salt" unless the context requires otherwise.

11
12 As used herein the term "C₁-C₆ alkyl" refers to a
13 straight or branched chain alkyl moiety having from
14 one to six carbon atoms, including for example,
15 methyl, ethyl, propyl, isopropyl, butyl, t-butyl,
16 pentyl and hexyl, and cognate terms. (such as "C¹-C⁶
17 alkoxy") are to be construed accordingly.

18
19 The term "C₁-C₆ alkenyl" refers to a straight or
20 branched chain alkyl moiety having one to six carbons
21 and having in addition one double bond, of either E or
22 Z stereochemistry where applicable. This term would
23 include, for example, an alpha, beta-unsaturated
24 methylene group, vinyl, 1-propenyl, 1- and 2-butenyl
25 and 2-methyl-2-propenyl.

26
27 The term "cycloalkyl" refers to a saturated
28 alicyclic moiety having from 3 to 8 carbon atoms
29 and includes for example, cyclopropyl, cyclobutyl,
30 cyclopentyl and cyclohexyl.

31
32
33

1 The term "cycloalkenyl" refers to an unsaturated
2 alicycle having from 3 to 8 carbon atoms and includes
3 cyclopropenyl, cyclobutenyl and cyclopentenyl,
4 cyclohexenyl.

5

6 The term "substituted", as applied to a phenyl or other
7 aromatic ring, means substituted with up to four
8 substituents each of which independently may be C₁-C₆
9 alkyl, C₁-C₆ alkoxy, hydroxy, thiol, C₁-C₆ alkylthiol,
10 amino, halo (including fluoro, chloro, bromo and iodo),
11 trifluoromethyl or nitro.

12

13 The term "amino acid side chain" means a characteristic
14 side chain attached to the -CH(NH₂)(COOH) moiety in the
15 following R or S amino acids: glycine, alanine, valine,
16 leucine, isoleucine, phenylalanine, tyrosine,
17 tryptophan, serine, threonine, cysteine, methionine,
18 asparagine, glutamine, lysine, histidine, arginine,
19 glutamic acid and aspartic acid.

20

21 The term "hydrocarbon chain" includes alkylene,
22 alkenylene and alkynylene chains of from 1 to 6 carbon
23 atoms. Preferably the carbon atom of the hydrocarbon
24 chain nearest to the hydroxamic acid group is a
25 methylene carbon atom.

26

27 There are several chiral centres in the compounds
28 according to the invention because of the presence of
29 asymmetric carbon atoms. The presence of several
30 asymmetric carbon atoms gives rise to a number of
31 diastereomers with the appropriate R or S
32 stereochemistry at each chiral centre. General formula
33 I and, where appropriate, all other formulae in this

1 specification are to be understood to include all such
2 stereoisomers and mixtures (for example racemic
3 mixtures) thereof. Compounds in which the chiral centre
4 adjacent the substituent R³ has S stereochemistry
5 and/or the chiral centre adjacent the substituent R²
6 has R stereochemistry are preferred.

7
8 Further or other preferred compounds include those in
9 which, independently or in any combination:

10
11 R¹ represents a hydrogen atom or a C₁-C₄ alkyl,
12 phenyl, thiophenyl, benzyl, acetyl or benzoyl
13 group;

14
15 R² represents a C₃-C₆ alkyl (for example isobutyl)
16 group;

17
18 R³ represents a benzyl or 4-(C₁-C₆)alkoxyphenylmethyl
19 or benzyloxybenzyl group;

20
21 R⁴ represents a C₁-C₄ alkyl (for example methyl)
22 group; and

23
24 R⁵ represents a hydrogen atom.

25
26 Particularly preferred compounds include:

27
28 1. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
29 methyl)-succinyl]-L-phenylalanine-N-methylamide,

30
31 2. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-
32 thio-methyl)succinyl]-L-phenylalanine-
33 N-methylamide,

- 1 3. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthio-
2 methyl) succinyl]-L-phenylalanine-N-methylamide,
3
- 4 4. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthio-
5 methyl) succinyl]-L-phenylalanine-N-methylamide and
6
- 7 5. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethyl)
8 succinyl]-L-phenylalanine-N-methylamide
9
- 10 6. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzoylthio-
11 methyl) succinyl]-L-phenylalanine-N-methylamide
12
- 13 7. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloyl-
14 thiomethyl) succinyl]-L-phenylalanine-N-methyl-
15 amide
16
- 17 8. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenyl-
18 thiomethyl) succinyl]-L-phenylalanine-N-methyl-
19 amide sodium salt
20
- 21 9. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxy-
22 phenyl-thiomethyl) succinyl]-L-phenylalanine-N-
23 methylamide
24
- 25 10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxy-
26 phenylthiomethyl) succinyl]-L-phenylalanine-N-
27 methylamide
28
- 29 11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thio-
30 phenethiomethyl) succinyl]-L-phenylalanine-N-
31 methylamide sodium salt
32
- 33

1 12. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxy-
2 phenylthiomethyl)succinyl]-L-phenylalanine-N-
3 methylamide sodium salt
4

5 13. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tert-
6 butylphenylthiomethyl)succinyl]-L-phenylalanine-
7 N-methylamide
8

9 14. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-di-
10 methylphenylthiomethyl)succinyl]-L-phenyl-
11 alanine-N-methylamide
12

13 15. bis-S,S'-{[4-(N-Hydroxyamino)-2R-isobutyl-
14 3S-(thiomethyl)succinyl]-L-phenylalanine-N-methyl-
15 amide} disulphide
16

17 16. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromo-
18 phenylthio-methyl)succinyl]-L-phenylalanine-N-
19 methylamide
20

21 17. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chloro-
22 phenylthiomethyl)succinyl]-L-phenylalanine-N-
23 methylamide
24

25 18. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methyl-
26 phenylthiomethyl)succinyl]-L-phenylalanine-N-
27 methylamide
28

29 19. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-
30 aminophenylthiomethyl)succinyl]-L-phenylalanine-
31 N-methylamide
32
33

- 1 20. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-
2 sulphinylmethylsuccinyl]-L-phenylalanine-N-methyl-
3 amide
- 4
- 5 21. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-
6 sulphinylmethylsuccinyl]-L-phenylalanine-N-methyl-
7 amide
- 8
- 9 22. [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenyl-
10 sulphinylmethylsuccinyl]-L-phenylalanine-N-
11 methylamide
- 12
- 13 23. [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenyl-
14 sulphinylmethylsuccinyl]-L-phenylalanine-N-
15 methylamide
- 16
- 17 24. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-
18 sulphinylmethylsuccinyl]-L-phenylalanine-N-
19 methylamide sodium salt
- 20
- 21 25. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyl-
22 oxycarbonylamino)phenyl)thiomethylsuccinyl]-L-
23 phenylalanine-N-methylamide
- 24
- 25 26. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-
26 (tert-butoxycarbonyl)-glycylamino)phenyl)thio-
27 methylsuccinyl]-L-phenylalanine-N-methylamide
- 28
- 29 and, where appropriate, their salts. Compounds 2 and 5
30 are especially preferred and compound 2 is the most
31 preferred, because of its good collagenase-inhibiting
32 and proteoglycanase-inhibiting activities.
- 33

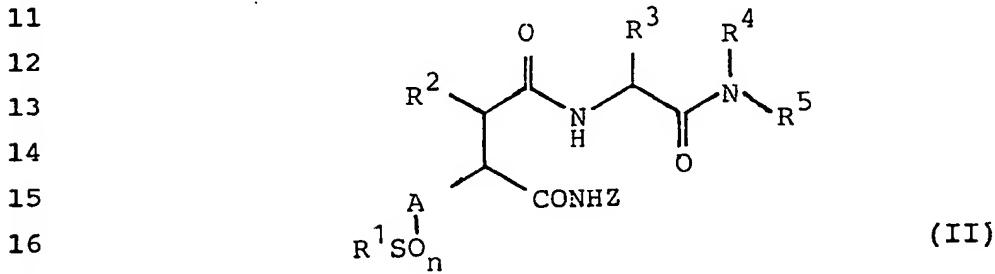
1 Compounds of general formula I may be prepared by any
 2 suitable method known in the art and/or by the
 3 following process, which itself forms part of the
 4 invention.

5

6 According to a second aspect of the invention, there is
 7 provided a process for preparing a compound of general
 8 formula I as defined above, the process comprising:

9

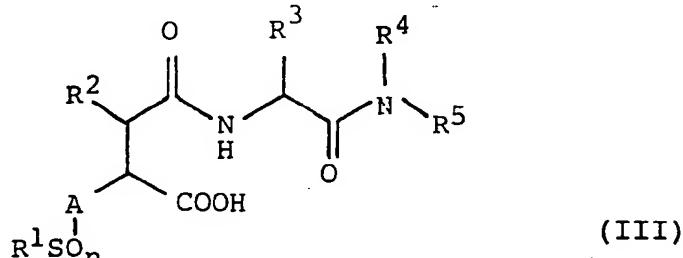
10 (a) deprotecting a compound of general formula II



wherein:

R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
 general formula I and Z represents a protective
 group such as a benzyl group; or

(b) reacting a compound of general formula III



wherein:

1 R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
2 general formula I,

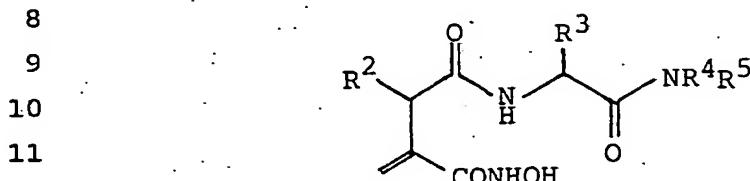
3

4 with hydroxylamine or a salt thereof; or

5

6 (c) reacting a compound of general formula VIA

7



(VIA)

wherein

15

16 R^2 , R^3 , R^4 and R^5 are as defined in general
17 formula I,

18

19 either with a thiol of the general formula R^1S , wherein
20 R^1 is as defined in general formula I to give a
21 compound of general formula I in which A represents a
22 methylene group and n is 0,

23

24 or with a cuprate of the general formula $(R^1S-A^1)_2CuLi$,
25 wherein R^1 is as defined in general formula I and A^1 is
26 such that $-A^1-CH_2-$ is identical to $-A-$, as defined in
27 general formula I.

28

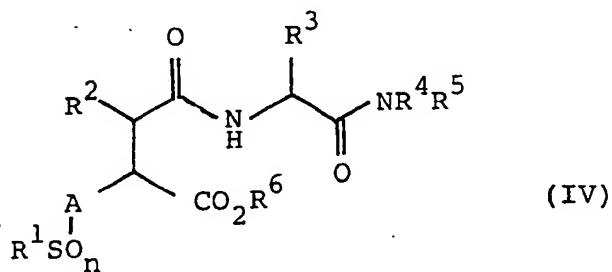
29 (d) optionally after step (a), step (b) or step (c)
30 converting a compound of general formula I into another
31 compound of general formula I.

32

33

1 Compounds of general formula I which are sulphoxides or
 2 sulphones can be derived from thiol compounds of
 3 general formula I by oxidation. Alternatively, thiols
 4 of general formula II or III may be oxidised.
 5 Compounds of general formula I which are disulphides
 6 (ie compounds wherein R¹ represents SR^X) may be derived
 7 from thiol esters of general formula I by milk
 8 oxidation, for example in air.

9
 10 A compound of general formula II may be prepared from a
 11 compound of general formula III by reaction with an
 12 O-protected (such as benzyl) hydroxylamine. A compound
 13 of general formula III may be prepared by
 14 desterification (such as hydrolysis) of an ester of the
 15 general formula IV



22 wherein:

23
 24 R¹, R², R³, R⁴, R⁵, A and n are as defined in
 25 general formula I and R⁶ represents C₁-C₆ alkyl,
 26 phenyl C₁-C₆ alkyl or substituted phenyl C₁-C₆
 27 alkyl.

28
 29 A compound of general formula IV can be prepared from
 30 an ester of general formula V or an acid of general
 31 formula VI

32
 33

1

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8

9 wherein:

10

11 R^2 , R^3 , R^4 and R^5 are as defined in general
12 formula I and R^6 represents C_1-C_6 alkyl, phenyl
13 C_1-C_6 alkyl or substituted phenyl C_1-C_6 alkyl

14

15 by reaction with a thiol R^1SH , wherein R^1 is as defined
16 in general formula I, to give compounds wherein A
17 represents a methylene group,

18

19 or by reaction with a cuprate of the general formula
20 $(R^1S-A^1)_2CuLi$, wherein R^1 is as defined in general
21 formula I and A^1 is such that $-A^1-CH_2-$ is identical to
22 $-A-$, as defined in general formula I.

23

24 Esters of general formula V can be prepared by
25 esterifying acids of general formula VI with an
26 appropriate alcohol R^6OH or other esterifying agent.

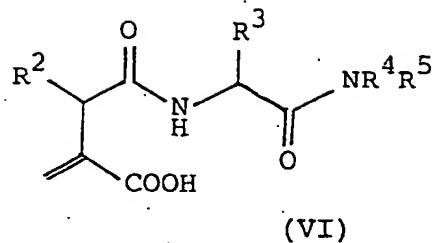
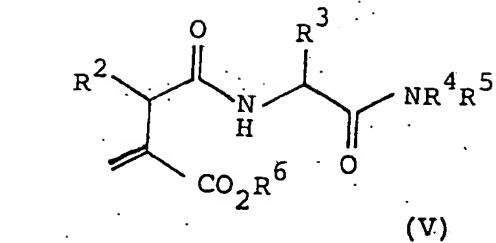
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28 Compounds of general formula VIA can be prepared by
29 reacting compounds of general formula VI with
30 hydroxylamine or a salt thereof.

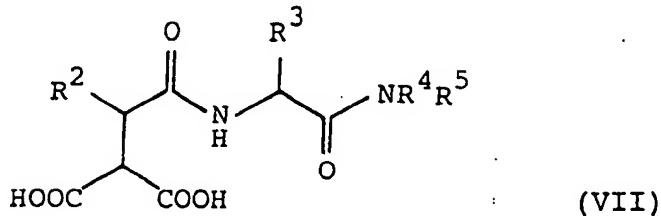
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32

33



1 An acid of general formula VI can be prepared by
 2 reacting a malonic acid derivative of general formula
 3 VII

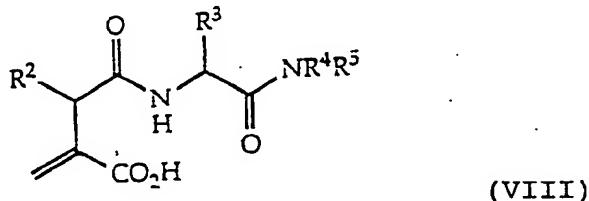


wherein:

R^2 , R^3 , R^4 and R^5 are as defined in general formula I

with formaldehyde in the presence of pyridine.

An acid of general formula VII can in turn be prepared by desterifying (for example hydrolysing) a compound of general formula VIII



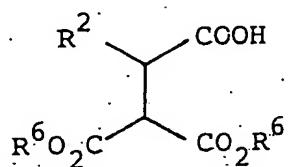
wherein:

R^2 , R^3 , R^4 and R^5 are as defined in general formula I and R^6 represents C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or substituted phenyl C_1-C_6 alkyl.

1 A compound of general formula VIII can be prepared by
 2 reacting a compound of general formula IX with a
 3 compound of general formula X

4

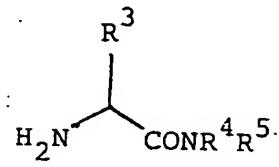
5



6

(IX)

7



(X)

8

9 wherein:

10

11 R^2 , R^3 , R^4 and R^5 are as defined in general
 12 formula I and R^6 represents $\text{C}_1\text{-C}_6$ alkyl, phenyl
 13 $\text{C}_1\text{-C}_6$ alkyl or substituted phenyl $\text{C}_1\text{-C}_6$ alkyl.

14

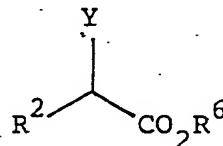
15 The starting materials and other reagents are either
 16 available commercially or can be synthesised by simple
 17 chemical procedures.

18

19 For example, a substituted acid of general formula IX
 20 may be prepared by reacting an ester of the general
 21 formula XI

22

23



24

(XI)

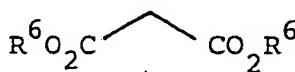
25

26 wherein Y represents halo and R^5 is as defined above
 27 and R^2 and R^6 as defined above, with a malonate
 28 derivative of the general formula XII

29

30

31



(XII)

32

33

1 wherein R^6 is as defined above with the proviso that
2 when R^6 is aromatic in general formula XI it is
3 aliphatic in general formula XII or vice versa, and
4 selectively de-esterifying.

5

6 Compounds of general formula XI can simply be derived
7 from amino acids, which can be obtained in
8 enantiomerically pure form, enabling a choice of
9 optically active compounds of general formula I to be
10 prepared.

11

12 Compounds of general formulae II and III are valuable
13 intermediates in the preparation of compounds of
14 general formula I. According to a third aspect of the
15 invention, there is therefore provided a compound of
16 general formula II. According to a fourth aspect of the
17 invention, there is provided a compound of general
18 formula III.

19

20 As mentioned above, compounds of general formula I are
21 useful in human or veterinary medicine as they are
22 active inhibitors, of metalloproteases involved in
23 tissue degradation.

24

25 According to a fifth aspect of the invention, there is
26 provided a compound of general formula I for use in
27 human or veterinary medicine, particularly in the
28 management (by which is meant treatment or prophylaxis)
29 of disease involving tissue degradation, in particular
30 rheumatoid arthritis, and/or in the promotion of wound
31 healing.

32

33

1 According to a sixth aspect of the invention, there is
2 provided the use of a compound of general formula I in
3 the preparation of an agent for the management of
4 disease involving tissue degradation, particularly
5 rheumatoid arthritis, and/or in the promotion of wound
6 healing. Compounds of general formula I can therefore
7 be used in a method of treating disease involving
8 tissue degradation, particularly rheumatoid arthritis,
9 and/or in a method of promoting wound healing, the
10 method in either case comprising administering to a
11 human or animal patient an effective amount of a
12 compound of general formula I.

13

14 The potency of compounds of general formula I to act
15 as inhibitors of collagenase (a metalloprotease
16 involved in tissue degradation) was determined by the
17 procedure of Cawston and Barrett, (Anal. Biochem., 99,
18 340-345, 1979) and their potency to act as inhibitors
19 of stromelysin was determined using the procedure of
20 Cawston *et al* (Biochem. J., 195, 159-165 1981), both of
21 which techniques are to be described more fully in the
22 examples and are incorporated by reference herein so
23 far as the law allows.

24

25 According to a seventh aspect of the invention, there
26 is provided a pharmaceutical or veterinary formulation
27 comprising a compound of general formula I and a
28 pharmaceutically and/or veterinarily acceptable
29 carrier. One or more compounds of general formula I may
30 be present in association with one or more non-toxic
31 pharmaceutically and/or veterinarily acceptable
32 carriers and/or diluents and/or adjuvants and if
33 desired other active ingredients.

1 According to an eighth aspect of the invention, there
2 is provided a process for the preparation of a
3 pharmaceutical or veterinary formulation in accordance
4 with the seventh aspect, the process comprising
5 admixing a compound of general formula I and a
6 pharmaceutically and/or veterinarily acceptable
7 carrier.

8

9 Compounds of general formula I may be formulated for
10 administration by any route and would depend on the
11 disease being treated. The compositions may be in
12 the form of tablets, capsules, powders, granules,
13 lozenges, liquid or gel preparations, such as oral,
14 topical, or sterile parenteral solutions or
15 suspensions.

16

17 Tablets and capsules for oral administration may be in
18 unit dose presentation form, and may contain
19 conventional excipients such as binding agents, for
20 example syrup, acacia, gelatin, sorbitol, tragacanth,
21 or polyvinyl-pyrollidone; fillers for example lactose,
22 sugar, maize-starch, calcium phosphate, sorbitol or
23 glycine; tabletting lubricant, for example magnesium
24 sterate, talc, polyethylene glycol or
25 silica; disintegrants, for example potato starch, or
26 acceptable wetting agents such as sodium lauryl
27 sulphate. The tablets may be coated according to
28 methods well known in normal pharmaceutical practice.
29 Oral liquid preparations may be in the form of, for
30 example, aqueous or oily suspensions, solutions,
31 emulsions, syrups or elixirs, or may be presented as a
32 dry product for reconstitution with water or other
33 suitable vehicle before use. Such liquid

1 preparations may contain conventional additives such
2 as suspending agents, for example sorbitol, syrup,
3 methyl cellulose, glucose syrup, gelatin,
4 hydrogenated edible fats; emulsifying agents, for
5 example lecithin, sorbitan monooleate, or acacia;
6 non-aqueous vehicles (which may include edible
7 oils); for example almond oil, fractionated coconut
8 oil, oily esters such as glycerine, propylene glycol,
9 or ethyl alcohol; preservatives, for example methyl or
10 propyl p-hydroxybenzoate or sorbic acid, and if
11 desired conventional flavouring or colouring agents.

12

13 The dosage unit involved in oral administration may
14 contain from about 1 to 250 mg, preferably from about
15 25 to 250 mg of a compound of general formula I. A
16 suitable daily dose for a mammal may vary widely
17 depending on the condition of the patient. However,
18 a dose of a compound of general formula I of about 0.1
19 to 300mg/kg body weight, particularly from about 1 to
20 100 mg/kg body weight may be appropriate.

21

22 For topical application to the skin the drug may be
23 made up into a cream, lotion or ointment. Cream or
24 ointment formulations that may be used for the drug
25 are conventional formulations well known in the art,
26 for example, as described in standard text books of
27 pharmaceutics such as the British Pharmacopoeia.

28

29 For topical applications to the eye, the drug may be
30 made up into a solution or suspension in a suitable
31 sterile aqueous or non-aqueous vehicle. Additives,
32 for instance buffers such as sodium metabisulphite or
33 disodium edeate; preservatives including bactericidal

1 and fungicidal agents, such as phenyl mercuric
2 acetate or nitrate, benzalkonium chloride or
3 chlorohexidine, and thickening agents such as
4 hypromellose may also be included.

5

6 The dosage employed for the topical administration
7 will, of course, depend on the size of the area being
8 treated. For the eyes each dose will be typically in
9 the range from 10 to 100 mg of the compound of general
10 formula I.

11

12 The active ingredient may also be administered
13 parenterally in a sterile medium. The drug
14 depending on the vehicle and concentration used, can
15 either be suspended or dissolved in the vehicle.
16 Advantageously, adjuvants such as a local anesthetic,
17 preservative and buffering agents can be dissolved in
18 the vehicle.

19

20 For use in the treatment of rheumatoid arthritis the
21 compounds of this invention can be administered by
22 the oral route or by injection intra-articularly into
23 the affected joint. The daily dosage for a 70 kg
24 mammal will be in the range of 10 mgs to 1 gram of a
25 compound of general formula I.

26

27 The following examples illustrate the invention, but
28 are not intended to limit the scope in any way. The
29 following abbreviations have been used in the
30 Examples:-

31

32

33

1 DCC - Dicyclohexylcarbodiimide
 2 DCM - Dichloromethane
 3 DCU - Dicyclohexylurea
 4 DIPE - Diisopropyl ether
 5 DMF - N,N-dimethylformamide
 6 HOBT - Hydroxybenztriazole
 7 NMM - N-Methylmorpholine
 8 TFA - Trifluoroacetic acid
 9 THF - Tetrahydrofuran
 10 WSCDI - N-(Dimethylaminoethyl)-N'-ethylcarbodiimide

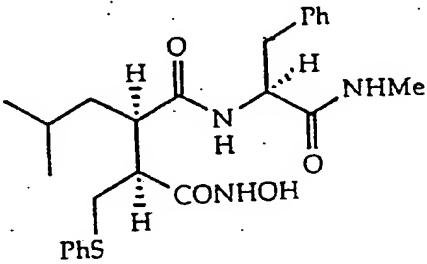
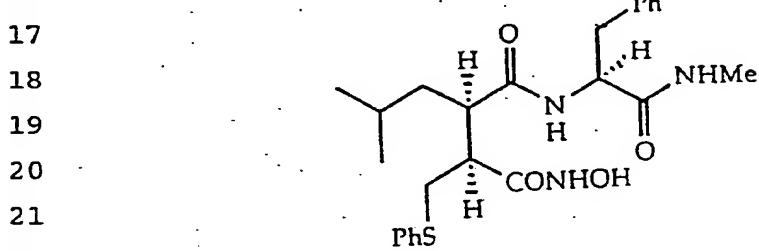
11

12 Example 1

13

14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)-
 15 succinyl]-L-phenylalanine-N-methylamide

16



1 and the aqueous phase was washed with further portions
2 of DCM (5 x 250ml). The combined organic layers
3 were dried over magnesium sulphate then the solvent
4 removed to give the acid as a pale yellow oil (123.1g,
5 0.63 mol, 83%)

6

7 $[\alpha]_D = +38.0^\circ$ (c = 2, methanol)

8

9 δ_H (250 MHz, $CDCl_3$) 4.29 (1H, t, $J = 6.5Hz$,
10 $BrCHCO_2H$), 1.91 (2H, t, $J = 7Hz$, $CHCH_2CH$), 1.83 (1H, m,
11 Me_2CH), and 0.94 (6H, 2xd, $J = 7Hz$, $(CH_3)_2CH$)

12

13 b) tert-Butyl 2R-Bromo-5-methylpentanoate.

14

15 2R-Bromo-5-methylpentanoic acid (123g, 0.63 mol)
16 was dissolved in DCM (400ml) and the solution cooled
17 to -40° while isobutene was condensed in to roughly
18 double the volume. Maintaining the temperature at
19 -40° concentrated sulphuric acid (4ml) was added
20 dropwise. When the addition was complete the
21 reaction was allowed to warm to room temperature
22 overnight. The resultant solution was concentrated
23 to half the volume by removing the solvent at reduced
24 pressure, then the DCM was washed twice with an equal
25 volume of 10% sodium bicarbonate solution. The organic
26 layer was dried over magnesium sulphate and the
27 solvent removed under reduced pressure to leave the
28 title compound as a yellow oil (148.0g, 0.59 mol, 94%).

29

30 $[\alpha]_D = +23.0^\circ$ (c = 2, methanol)

31

32

33

1 delta_H (250 MHz, CDCl₃) 4.18 (1H, t, J= 6.5Hz,
2 BrCHCO₂H), 1.89 (2H, m, CHCH₂CH), 1.78 (1H, m, Me₂CH),
3 1.49 (9H, s, (CH₃)₃C) and 0.94 (6H, 2xd, J= 7Hz,
4 (CH₃)₂CH)

5

6 delta_C (63.9 MHz, CDCl₃) 167.0, 82.0, 46.3, 43.4,
7 27.6, 26.3, 22.2, and 21.6.

8

9 c) Benzyl (2-benzloxycarbonyl-3R-(tert-butoxycarbonyl)-
10 5-methylhexanoate.

11

12 Dibenzyl malonate (124.5g, 0.44 mol) was taken up in
13 dry DMF and potassium tert-butoxide (49.2g, 0.44
14 mol) was added portionwise with stirring and cooling.
15 When a homogeneous solution had formed it was cooled to
16 0° then tert-butyl-2R-bromo-5-methylpentanoate
17 (110.0g, 0.44 mol) in DMF (200 ml) was added dropwise
18 over 1h. When addition was complete the reaction was
19 transferred to a cold room at <5° and left for 4 days.
20 The reaction mixture was partitioned between ethyl
21 acetate and saturated ammonium chloride then the
22 aqueous layer extracted with further ethyl acetate
23 (4x500ml), drying and solvent removal left an oil
24 (228g) heavily contaminated with DMF. This oil was
25 taken into ether (1 litre) and washed with brine
26 (2x1l) then the organic layer dried (magnesium
27 sulphate), solvent removed under reduced pressure to
28 leave the desired material (179g) contaminated with a
29 small amount of dibenzyl malonate.

30

31 [alpha]_D = +22.5° (c = 2, methanol)

32

33

1 δ_H (250 MHz, $CDCl_3$) 7.40 - 7.25 (10H, m, Aromatic
2 H), 5.14 (4H, 2xABq, CH_2Ph), 3.77 (1H, d, $J = 10Hz$,
3 BnO_2CCHCO_2Bn), 3.09 (1H, dt, $J = 10, 6Hz$,
4 CH_2CHCO_2tBu), 1.50 (3H, m, $CH_2 + CHMe_2$) 1.41 (9H, s,
5 $C(CH_3)_3$) and 0.88 (6H, 2xd, $J = 7Hz$).

6

7 d) [4-Benzylxy-3-benzylxycarbonyl-2R-isobutyl-
8 succinyl]-L-phenylalanine-N-methylamide

9

10 Benzyl(2-benzylxycarbonyl-5-methyl-3R-tert-butoxycarb-
11 onyl)-hexanoate (281.4g, 0.56 mol) was taken up in 5%
12 water in TFA (410 ml) and allowed to stand at 5°
13 overnight. After this time the TFA was evaporated
14 under reduced pressure then the residue partitioned
15 between DCM (1l) and brine (200ml). Solvent removal
16 left an oil which crystallised on standing (230g).

17

18 The crude acid from this reaction was dissolved in DMF
19 (1l), then HOBT (95.3g, 0.64 mol), NMM (64g, 0.64 mol)
20 and phenylalanine-N-methylamide (113.0g, 0.64 mol) were
21 added at room temperature. The mixture was cooled
22 to 0° before dropwise addition of DCC (131.0g, 0.64
23 mol) in THF (1l). This solution was stirred to room
24 temperature over the weekend. The precipitated DCU was
25 removed by filtration then the solvents were removed
26 from the filtrate under reduced pressure to leave an
27 oil. This oily residue was dissolved in ethyl acetate
28 then washed with 10% citric acid, 10% sodium
29 bicarbonate and saturated brine. The organic layer was
30 dried (magnesium sulphate), filtered then the solvent
31 removed under reduced pressure to give the title
32 compound as an oil (400g). This material was columned
33 on silica using gradient elution (0 - 50% ethyl

1 acetate in hexane) to remove impurities and separate
2 a small amount of the minor diastereoisomer. The
3 material from the column (195g) was recrystallised
4 from DIPE to give the title compound as a white
5 crystalline solid (140.2g, 0.25 mol, 47%)

6

7 m.p. 98 -99°

8 Analysis calculated for $C_{33}H_{38}N_2O_6$

9 Requires C 70.95 H 6.86 N 5.01

10 Found C 70.56 H 6.89 N 5.06

11

12 δ_H (250MHz, $CDCl_3$) 7.42 - 7.13 (15H, m, Aromatic
13 H), 6.58 (1H, d, $J=7.7Hz$, $CONH$), 5.75 (1H, m,
14 $CONHMe$), 5.20 - 5.05 (4H, m, OCH_2Ph), 4.50 (1H, dt, $J=$
15 6.9, 7.7Hz, $CHCH_2Ph$), 3.79 (1H, d, $J= 9.1Hz$,
16 $CH(CO_2Bn)$), 3.15 - 2.91 (2H, m, CH_2Ph), 2.65 (3H, d, $J=$
17 4.8Hz, $CONHCH_3$), 1.52 (1H, m, $CHCH_2CH$), 1.32 (1H, m,
18 $CH(CH_3)$), 1.05 (1H, m, $CHCH_2CH$), and 0.74 (6H, 2xd, $J=$
19 6.5Hz, $CH(CH_3)_2$)

20

21 e) [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-
22 alanine-N-methylamide.

23

24 [4-Benzyl-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-
25 L-phenylalanine-N-methylamide (29.6g, 53mmol) was taken
26 up in ethanol, ammonium formate (16.7g, 265mmol) added
27 followed by 10% palladium on charcoal (6g) as a
28 slurry in isopropyl alcohol. After 30 minutes at room
29 temperature the catalyst was removed by filtration,
30 then washed with ethanol to give a solution of the
31 crude diacid. To this was added piperidine (5.0g) and
32 the mixture stirred at room temperature for 15 minutes
33 before addition of aqueous formaldehyde (40%

1 solution, 25ml). After 18 hours at room temperature
2 the mixture was refluxed for 1 h. Solvents were
3 removed under reduced pressure and the residue
4 partitioned between ethyl acetate and citric acid.
5 The acid layer was extracted with further portions of
6 ethyl acetate (2x250ml), the combined organic layers
7 were extracted with potassium carbonate (3x200ml).
8 These base extracts were acidified to pH 4 and
9 re-extracted with DCM then the organic layer dried
10 over magnesium sulphate. Solvent removal
11 under reduced pressure gave the desired product as a
12 white solid (9.35g, 27.0mmol, 51%).

13

14 m.p. 149-151°C

15

16 δ_H (250MHz, $CDCl_3$) 8.37 (2H, d, $J = 9.0Hz$, CONH),
17 7.39 (1H, m, CONHMe), 7.27 - 7.06 (5H, m, Aromatic
18 H), 6.40 (1H, s, CH_2CHCO_2H), 5.78 (1H, s, CH_2CHCO_2H),
19 4.93 (1H, q, $J = 7Hz$, $CHCH_2Ph$), 3.92 (1H, m, $CH_2CHCONH$),
20 2.95 (2H, m, CH_2Ph), 2.71 (3H, d, $J = 4.1Hz$, $NHCH_3$),
21 1.68 (1H, m), 1.45 (2H, m), and 0.86 (6H, 2xd, $J =$
22 5.8Hz, $CH(CH_3)_2$).

23

24 δ_C (63.9Hz, $CDCl_3$) 173.3, 172.8, 169.6, 139.1,
25 136.3, 129.2, 128.3, 127.0, 126.6, 54.4, 43.5, 41.4,
26 39.1, 26.2, 25.7, 22.5 and 22.4

27

28 f) [4-Hydroxy-2R-isobutyl-3S-(phenylthiomethyl)-
29 succinyl]-L-phenylalanine-N-methylamide

30

31 [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-
32 alanine-N-methylamide (15.0g, 44mmol) was dissolved in
33 thiophenol

1 (150ml) and the mixture stirred in the dark under
2 nitrogen at 60° for 2 days. Ether was added to the
3 cooled reaction mixture and the precipitated product
4 collected by filtration. The solid was washed with
5 large volumes of ether and dried under vacuum to give
6 the title compound (13.1g, 28.7mmol, 65%).

7

8 m.p. 199-201°C

9 Analysis calculated for C₂₅H₃₂N₂O₄S
10 Requires C 65.76 H 7.06 N 6.14 S 7.02
11 Found C 65.69 H 7.06 N 6.07 S 7.05

12

13 δ_H (250MHz, D₆-DMSO) 8.40 (1H, d, J= 9Hz, CONH),
14 7.82 (1H, m, CONHMe), 7.35 - 7.10 (7H, m, Aromatic
15 H), 7.04 (3H, m, Aromatic H), 4.62 (1H, m, CHCH₂Ph),
16 2.94 (1H, dd, J= 14,5Hz, CHCH₂Ph), 2.89 (1H, dd, J=
17 14,9Hz, CHCH₂Ph), 2.62 (3H, d, J= 4.5Hz, CONHCH₃), 2.41
18 (3H, m, 2xCH + CH₂SPh), 2.23 (1H, d, J= 12Hz, CH₂SPh),
19 1.43 (1H, m, CHCH₂CH), 1.30 (1H, bm, CH(CH₃)₂), 0.90
20 (1H, m, CHCH₂CH) and 0.78 (6H, 2xd, J= 6.5Hz, CH(CH₃)₂).
21

22 g). [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
23 methyl) succinyl]-L-phenylalanine-N-methylamide

24

25 [4-Hydroxy-2R-isobutyl-3S-(phenylthiomethyl)succinyl]-
26 L-phenylalanine-N-methylamide (16.8g, 37 mmol) and
27 HOBT (6.6g, 44 mmol) were dissolved in DCM / DMF
28 (4:1) and the mixture cooled to 0° before adding WSCDI
29 (8.5g, 44 mmol) and NMM (4.5g, 44 mmol). The mixture
30 was stirred at 0° for 1h to ensure complete formation
31 of the activated ester. Hydroxylamine hydrochloride
32 (3.8g, 55 mmol) and NMM (5.6g, 55 mmol) were dissolved
33 in DMF then this mixture added dropwise to the cooled

1 solution of the activated ester. After 1h the reaction
2 was poured into ether / water (1:1) whereupon the
3 desired product precipitated as white crystals. These
4 were collected by filtration, further washed with ether
5 and water then dried under vacuum at 50°. This
6 material was recrystallised from methanol / water (1:1)
7 to remove a trace of the minor diastereomer (9.03g,
8 19.2 mmol, 52%).

9

10 m.p. 227-229°C

11

12 $[\alpha]_D = -88^\circ$ (c = 10, methanol)

13

14 δ_H (250MHz, D_6 -DMSO) 8.84 (1H, d, $J = 1.5\text{Hz}$, NHOH),
15 8.35 (1H, d, $J = 8.7\text{Hz}$, CONH), 7.87 (1H, m, CONHMe),
16 7.29 - 6.92 (11H, m, Aromatic H + NHOH), 4.60 (1H, m,
17 CHCH_2Ph), 2.94 (1H, dd, $J = 13.5, 4.3$, CHCH_2Ph), 2.77
18 (1H, dd, $J = 13.5, 10$, CHCH_2Ph), 2.60 (3H, d, $J = 4.6\text{Hz}$),
19 2.53 (1H, m), 2.41 (1H, m), 2.20 (1H, dd, $J =$
20 $13.4, 2.2\text{Hz}$, CH_2SPh), 2.09 (1H, dd, $J = 13.4, 2.4\text{Hz}$,
21 CH_2SPh), 1.38 (2H, m, CHMe_2 + CHCH_2CH), 0.88 (1H,
22 m, CHCH_2CH), 0.82 (3H, d, $J = 6.4\text{Hz}$, $\text{CH}(\text{CH}_3)_2$), and 0.74
23 (3H, d, $J = 6.4\text{Hz}$, $\text{CH}(\text{CH}_3)_2$).

24

25 δ_C (63.9MHz, D_6 -DMSO) 172.9, 171.6, 166.3, 138.1,
26 136.7, 129.1, 128.9, 128.0, 127.3, 126.4, 125.2, 54.2,
27 46.4, 46.0, 37.7, 32.4, 25.6, 25.2, 24.2, and 21.7.

28

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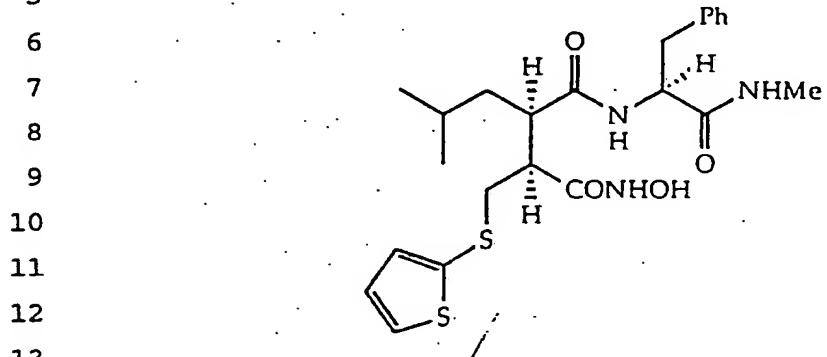
33

1 Example 2

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiometh-
4 yl) succinyl]-L-phenylalanine-N-methylamide

5

14 a) [4-N-Hydroxy-2R-isobutyl-3S-(thiophenylthiomethyl)
15 succinyl]-L-phenylalanine-N-methylamide

16

17 The title compound was prepared from
18 [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-
19 alanine-N-methylamide (400mg, 1.16mmol) by the method
20 described in example 1f, substituting thiophenethiol in
21 the place of thiophenol to give a material (320mg,
22 0.73mmol, 63%) with the following characteristics.

23

24 m.p. 184-186°C

25

26 delta_H (250MHz, D₆-DMSO) 8.29 (1H, d, J= 8.1Hz, CONH),
27 7.84 (1H, m, CONHMe), 7.57 (1H, d, J= 5.1Hz,
28 Thiophene H), 5H, m, Aromatic H), 7.00 (2H, m,
29 Thiophene H), 4.50 (1H, m, CHCH₂Ph), 2.91 (1H, m,
30 CHCH₂Ph), 2.75 (1H, m, CHCH₂Ph), 2.56 (3H, d, J=
31 4.0Hz, CONHCH₃), 2.34 (3H, m), 1.99 (1H, d, J= 9.3Hz,

32

33

1 $\underline{\text{CH}_2\text{SHet}}),$ 1.42 (1H, m, $\text{CHCH}_2\text{CH}),$ 1.29 (1H, bm,
2 $\text{CH}(\text{CH}_3)_2),$ 0.87 (1H, m, $\text{CHCH}_2\text{CH}),$ 0.79 (3H, d, J=
3 6.4Hz, $\text{CH}(\text{CH}_3)_2),$ and 0.72 (3H, d, J= 6.4Hz, $\text{CH}(\text{CH}_3)_2).$

4

5 b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthio-
6 methyl)succinyl]-L-phenylalanine-N-methylamide

7

8 Prepared by the method described in example 1g to
9 give material with the following characteristics

10

11 m.p. 236-238°C

12

13 Analysis calculated for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4\text{S}_2$

14 Requires C 57.84 H 6.54 N 8.80

15 Found C 57.64 H 6.48 N 8.85

16

17 δ_{H} (250MHz, D_6 -DMSO) 8.80 (1H, s, $\text{CONHOH}),$ 8.08
18 (1H, d, J=8Hz, $\text{CONH}),$ 7.52 (1H, m, $\text{CONHMe}),$ 7.32 (1H,
19 dd, J= 4.6,2.9Hz, Thiophene H), 7.17 - 6.95 (5H, m,
20 Aromatic H), 6.89 (2H, m, Thiophene H), 4.46 (1H,
21 m, $\text{CHCH}_2\text{Ph}),$ 2.89 (1H, dd, J=13.6,4.4Hz, $\text{CHCH}_2\text{Ph}),$ 2.72
22 (1H, dd, J= 13.6,10.5Hz, $\text{CHCH}_2\text{Ph}),$ 2.54 (3H, d, J=
23 4.3Hz, $\text{CONHCH}_3),$ 2.46 (1H, d, J= 12.1Hz, $\underline{\text{CH}_2\text{S}}),$ 2.35
24 (1H, bt, J= 10.2Hz), 2.14 (1H, bt, J= 10.2Hz), 1.98
25 (1H, dd, J=12.7,2.5Hz, $\text{CHCH}_2\text{Ph}),$ 1.35 (1H, bt, J=
26 11.4Hz, $\text{CHCH}_2\text{CH}),$ 1.22 (1H, bm, $\text{CH}(\text{CH}_3)_2),$ 0.86 (1H,
27 bt, J=12.6Hz, $\text{CHCH}_2\text{CH}),$ 0.74 (3H, d, J= 6.3Hz,
28 $\text{CH}(\text{CH}_3)_2),$ and 0.68 (3H, d, J= 6.4Hz, $\text{CH}(\text{CH}_3)_2).$

29

30 δ_{C} (63.9MHz, D_6 -DMSO) 172.5, 171.6, 166.1, 138.0,
31 133.8, 132.7, 129.4, 129.2, 128.1, 127.8, 126.5, 54.2,
32 46.2, 46.0, 38.5, 37.6, 25.8, 25.2, 24.2, and 21.7.

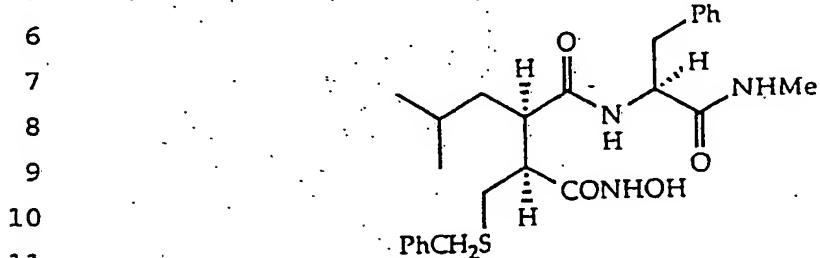
33

1 Example 3

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthiomethyl)
4 succinyl]-L-phenylalanine-N-methylamide

5



10

11

12

13 Prepared by the method described in example 1g to
14 give material with the following characteristics

15

16 m.p. °

17

18 Analysis calculated for C₂₇H₃₇N₃O₅S.0.5H₂O

19 Requires C 61.81 H 7.30 N 8.00

20 Found C 61.85 H 7.15 N 7.45

21

22 delta_H (250MHz, D₆-DMSO) 8.40 (1H, s, CONHOH), 8.22
23 (1H, m, NHMe), 7.20 (5H, m, Aromatic H), 6.58 (4H, m),
24 4.10 (1H, m, CHCH₂Ph), 3.22 (3H, s, OCH₃), 3.04 - 2.45
25 (4H, m, 2xCH₂Ar), 2.42 (3H, d, J= 6Hz, NHCH₃), 2.32 -
26 2.08 (4H, m), 0.78 (2H, m, CHCH₂CH), and 0.40 - 0.18
27 (7H, m, (CH₃)₂CH).

28

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32

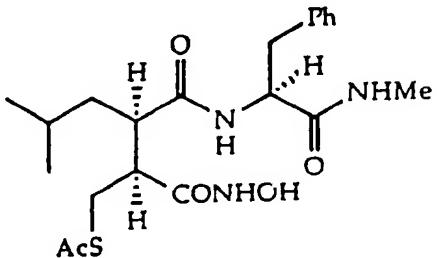
33

1 Example 4

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)
4 succinyl]-L-phenylalanine-N-methylamide

5



6

7

8

9

10

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12

13

14

Prepared by the method described in example 1g to
give material with the following characteristics

15

16 m.p. 226-227°C

17

18 Analysis calculated for C₂₁H₃₁N₃O₅S·H₂O

19 Requires C 55.37 H 7.30 N 9.22

20 Found C 55.57 H 6.99 N 9.53

21

22 delta_H (250MHz, D₆-DMSO) 8.84 (1H, s, NHOH), 8.36 (1H,
23 d, J= 8Hz, CONH), 7.80 (1H, d, J= 6Hz, NHMe), 7.20 (3H,
24 m, Aromatic H), 4.58 (1H, m, CHCH₂Ph), 3.16 - 2.62
25 (2H, m, CHCH₂Ph), 2.54 (3H, d, J= 4Hz, NHCH₃), 2.22
26 (3H, s, CH₃COS), 2.36 - 2.10 (4H, m, CHCHCH₂S), 1.36
27 (2H, m, CHCH₂CH), and 0.98 - 0.66 (7H, m, CH(CH₃)₂).

28

29

30

31

32

33

1 Example 5

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethyl)
4 succinyl]-L-phenylalanine-N-methylamide

5

6

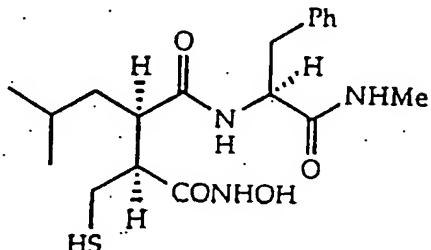
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11



12

13 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)
14 succinyl]-L-phenylalanine-N-methylamide (30mg,
15 0.06mmol) was stirred in methanol (3ml) with
16 methylamine (1ml methanolic solution) at room
17 temperature. After 30 minutes the crystalline
18 product (20mg, 0.05mmol, 74%) was filtered off and
19 dried.

20

21 m.p. 234°C

22 Analysis calculated for C₁₉H₃₉N₃O₄S.1.5H₂O

23 Requires C 54.10 H 7.63 N 9.94 S 7.60

24 Found C 54.28 H 7.16 N 10.43 S 7.80

25

26 delta_H (250MHz, D₆-DMSO) 8.28 (1H, d, J= 9Hz, NHOH),
27 7.80 (1H, m, NHMe), 7.22 (5H, m, Aromatic H), 4.60 (1H,
28 m, CHCH₂Ph), 3.08 - 2.56 (2H, m, CHCH₂Ph), 2.50 (3H, d,
29 J= 4Hz, NHCH₃), 2.40 - 2.02 (4H, m, CHCHCH₂SH), 1.44
30 - 1.22 (2H, m, CHCH₂CH) and 0.98 - 0.72 (7H, m,
31 CH(CH₃)₂).

32

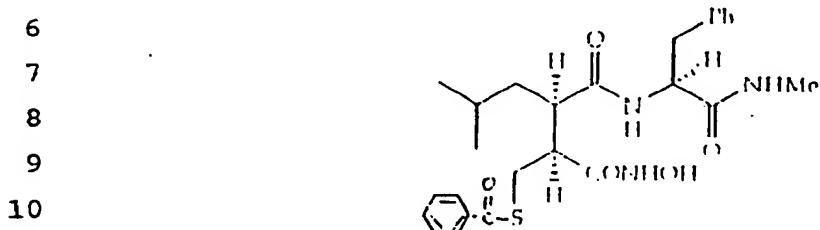
33

1 Example 6

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzoylthiomethyl)-
4 succinyl]-L-phenylalanine-N-methylamide

5



12

13 The title compound was prepared by the method described
14 in Example 1g to give material with the following
15 characteristics

16

17 m.p. 227 - 228°

18 Analysis calculated for C₂₁H₃₁N₃O₅S

19 Requires C 62.50 H 6.66 N 8.41

20 Found C 62.32 H 6.67 N 8.40

21

22 δ_{H} (250 MHz, CDCl₃:D₆DMSO (1:1)) 8.82 (1H, s,
23 NHOH), 8.25 (1H, d, J=8.4Hz, NHOH), 7.87 (2H, dd,
24 J=8.5, 1.1Hz), 7.60 (2H, m, Ar-H and CONH), 7.50 (2H,
25 t, J=8.2Hz), 7.28 (2H, d, J=8.4Hz), 7.16 (2H, t,
26 J=7.2Hz), 7.04 (1H, t, J=8.5Hz), 4.65 (1H, m, CHCH₂Ph),
27 3.06 (1H, dd, J=14.1, 5.0Hz, CHCH₂Ph), 2.90 (1H, dd,
28 J=13.9, 10Hz, CHCH₂Ph), 2.73 (2H, m SCH₂Ph), 2.65 (3H,
29 d, J=4.7Hz, NHMe), 2.33 (1H, dt, J=11.0, 4.7Hz), 1.51
30 (1H, t, J=7Hz, CH₂CHMe₂), 1.24 (1H, m, CHMe₂), 0.97
31 (1H, t, J=7Hz, CH₂CHMe₂), 0.84 (3H, d, J=6.5Hz, CHMe₂)
32 and 0.79 (3H, d, J=6.5Hz, CHMe₂).

33

1 Example 7

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloylthiomethyl)
4 succinyl]-L-phenylalanine-N-methylamide

5

6

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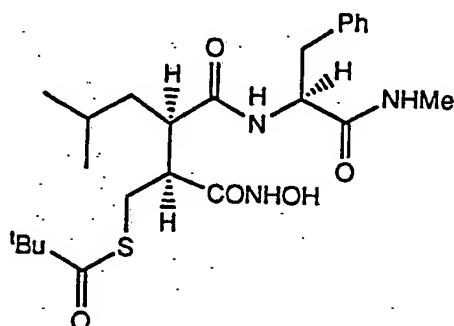
13

14

15 [4-Hydroxy-2R-isobutyl-3S-(pivaloylthiomethyl)
16 succinyl]-L-phenylalanine-N-methylamide (0.8g, 1.7
17 mmol) and HOBT (0.31g, 2.1 mmol) were dissolved in 1:1
18 DCM/DMF and the mixture cooled to 0°C before adding
19 WSCl (0.4g, 2.1mmol) and NMM (0.21g, 2.1mmol). The
20 mixture was stirred at 0°C for 1h to ensure complete
21 formation of the activated ester. Hydroxylamine
22 hydrochloride (0.18g, 2.6mmol) and NMM (0.26g, 2.6mmol)
23 were dissolved in DMF then this mixture was added
24 dropwise to the cooled solution of the activated ester.
25 After 1h the reaction was poured into ether/water (1:1)
26 whereupon the desired product precipitated as white
27 crystals. These were collected by filtration, further
28 washed with ether and water, then dried under vacuum at
29 50°C. This material was recrystallised from
30 methanol/water (1:1) to remove a trace of the minor
31 diastereomer (0.38g, 0.7mmol, 45%).

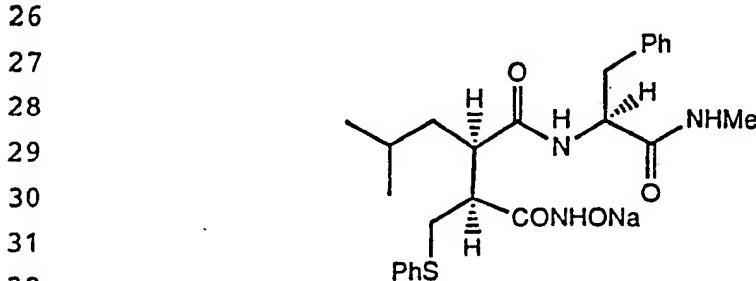
32

33 m.p. 225°C



1 [alpha]_D = -3.5° (c=2, methanol)
2
3 Analysis calculated for C₂₄H₃₉N₃O₅S.0.5 H₂O
4 Requires: C58.99 H7.84 N8.60
5 Found: C58.96 H7.63 N8.55
6
7 delta_H (250MHz, D₆-DMSO) 8.81 (1H, s, J = 1.5Hz, NHOH),
8 8.30 (1H, d, J=8Hz, CONH), 7.78 (1H, d, J=6Hz, CONHMe),
9 7.27-7.03 (5H, m, aromatic H), 4.54 (1H, m, CHCH₂Ph),
10 2.94 (1H, dd, J = 12,5Hz, CHCH₂Ph), 2.79 (1H, dd, J =
11 13,10Hz, CHCH₂Ph) 2.56 (3H, d, J = 4.5Hz, NHCH₃), 2.44
12 (2H, m), 2.20 (1H, dd, J = 13,3Hz, CH₂S), 2.07 (1H,
13 dt), 1.36 (2H, m), 1.13 (9H, s, C(CH₃)₃), 0.87 (1H, m,
14 CH₂CH(CH₃)₂), 0.79 (3H, d, J = 6Hz, CH(CH₃)₂), and 0.74
15 (3H, d, J = 6Hz, CH(CH₃)₂).
16
17 delta_C (63.9MHz, D₆-DMSO) 172.55, 171.59, 168.24,
18 138.03, 129.18, 128.00, 126.24, 54.21, 46.48, 45.84,
19 45.55, 37.61, 28.30, 27.13, 25.64, 25.25, 24.24, and
20 21.63.

21
22 Example 8
23
24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)
25 succinyl]-L-phenylalanine-N-methylamide sodium salt



1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)
2 succinyl]-L-phenylalanine-N-methylamide (0,2g, 0.4
3 mmol) was dissolved in 20ml of methanol and 1eq of 0.1N
4 NaOH(aq) added. The solvent was removed in vacuo and
5 the residue dissolved in water and freeze-dried
6 (0.21g, 0.4 mmol, 100%).

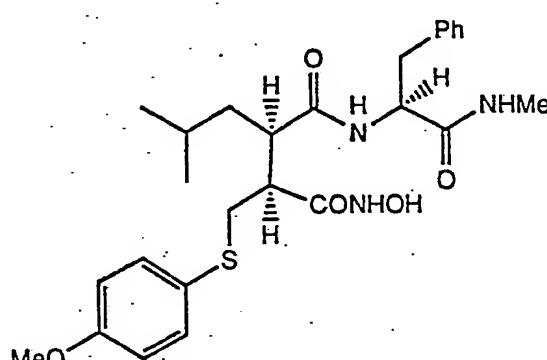
7 m.p. 184°C
8

9 [alpha]_D = -7.7° (c=2, methanol)
10

11 delta_H (250MHz, D₆-DMSO) 8.62 (1H, s, J = 1.5Hz, NHOH),
12 8.28 (1H, d, J = 8Hz, CONH), 7.26 - 7.04 (10H, m,
13 aromatic H), 4.43 (1H, m, CHCH₂Ph), 3.00 (1H, dd, J =
14 14,4Hz, CHCH₂Ph), 2.84 (1H, dd, J = 14,10Hz, CHCH₂Ph),
15 2.55 (3H, d, J = 4.5Hz, NHCH₃), 2.46 (3H, m), 2.21 (1H,
16 m), 1.39 (1H, m), 1.14 (1H, m), 1.00 (1H, m), and 0.70
17 (6H, d, J = 5.7Hz)
18

19 Example 9
20

21 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-
22 thiomethyl)]
23



1 succinyl]-L-phenylalanine-N-methylamide[4-Hydroxy-2R-
2 isobutyl-3S-(4-methoxyphenylthiomethyl)succinyl]-L-
3 phenylalanine-N-methylamide (0.5g, 1 mmol) and HOBT
4 (0.18g, 1.2 mmol) were dissolved in 1:1 DCM/DMF and the
5 mixture cooled to 0°C before adding WSDCI (0.23g,
6 1.2mmol) and NMM (0.12g, 1.2mmol). The mixture was
7 stirred at 0°C for 1h to ensure complete formation of
8 the activated ester. Hydroxylamine hydrochloride (0.1g,
9 1.5mmol) and NMM (0.15g, 1.5mmol) were dissolved in DMF
10 then this mixture was added dropwise to the cooled
11 solution of the activated ester. After 1h the reaction
12 was poured into ether/water (1:1) whereupon the desired
13 product precipitated as white crystals. These were
14 collected by filtration, further washed with ether and
15 water, then dried under vacuum at 50°C. This material
16 was recrystallised from methanol/water (1:1) to remove
17 a trace of the minor diastereomer (0.36g, 0.7mmol,
18 72%).

19 m.p. 225°C

21 [alpha]_D = +8° (c=0.5, methanol)

23 Analysis calculated for C₂₆H₃₅N₃O₅S

24 Requires: C62.25 H7.04 N8.38

25 Found: C62.43 H7.09 N8.37

27 delta_H (250MHz, D₆-DMSO) 8.83 (1H, s, J = 1.5Hz, NHOH),
28 8.28 (1H, d, J = 8Hz, CONH), 7.83 (1H, d, J = 6Hz,
29 CONHMe), 7.28 - 6.86 (9H, m, aromatic H), 4.52 (1H, m,
30 CHCH₂Ph), 3.73 (3H, s, OCH₃), 2.91 (1H, dd, J = 14,4Hz,
31 CHCH₂Ph), 2.75 (1H, dd, J = 14,10Hz, CHCH₂Ph), 2.57
32 (3H, d, J = 4.5Hz, NHCH₃), 2.50 - 2.34 (2H,m), 2.16 -
33

1 1.99 (2H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$) 1.36 (2H, m), 0.88 (1H, m,
 2 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.80 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$), and 0.73
 3 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$).

4

5 δ_{C} (63.9MHz, $\text{D}_6\text{-DMSO}$) 172.79, 171.62, 168.39,
 6 138.14, 131.34, 129.19, 128.00, 126.44, 114.59, 55.32,
 7 54.20, 38.68, 25.63, 25.17, 24.26, and 21.70.

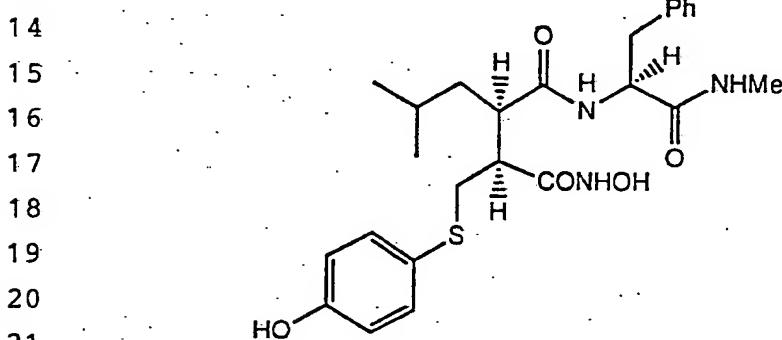
8

9 Example 10

10

11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
 12 thiomethyl) succinyl]-L-phenylalanine-N-methylamide

13



1 whereupon the desired product precipitated as white
2 crystals. These were collected by filtration, further
3 washed with ether and water, then dried under vacuum at
4 50°C. This material was recrystallised from
5 methanol/water (1:1) to remove a trace of the minor
6 diastereomer (0.13g, 0.2mmol, 31%).

7

8 m.p. 216°C

9

10 $[\alpha]_D = -65^\circ$ (c=0.5, methanol)

11

12 Analysis calculated for $C_{25}H_{33}N_3O_5S$

13 Requires: C61.58 H6.82 N8.62

14 Found: C61.43 H6.81 N8.08

15

16 δ_H (250MHz, D_6 -DMSO) 8.82 (1H, s, $J = 1.5\text{Hz}$, $NHOH$),
17 8.26 (1H, d, $J = 8\text{Hz}$, $CONH$), 7.81 (1H, d, $J = 6\text{Hz}$,
18 $CONHMe$), 7.27 - 6.64 (9H, m, aromatic H), 4.49 (1H, m,
19 $CHCH_2Ph$), 2.90 (1H, dd, $J=14,4\text{Hz}$, $CHCH_2Ph$), 2.74 (1H,
20 dd, $J=14,10\text{Hz}$, $CHCH_2Ph$), 2.57 (3H, d, $J = 4.5\text{Hz}$,
21 $NHCH_3$), 2.54 - 2.29 (2H, m), 2.14 - 1.98 (2H, m,
22 $CH_2CH(CH_3)_2$), 1.35 (2H, m), 0.88 (1H, m, $CH_2CH(CH_3)_2$),
23 0.80 (3H, d, $J = 6\text{Hz}$, $CH(CH_3)_2$), and 0.73 (3H, d, $J =$
24 6Hz, $CH(CH_3)_2$).

25

26 $\delta_{^13C}$ (63.9MHz, D_6 -DMSO) 172.81, 171.66, 168.46,
27 156.50, 133.02, 132.17, 129.17, 128.02, 126.44, 124.17,
28 116.00, 54.20, 46.35, 46.13, 37.59, 35.40, 25.62,
29 25.16, 24.27, and 21.69.

30

31

32

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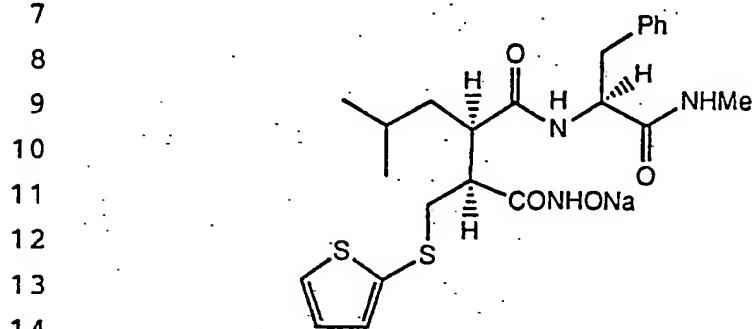
1 Example 11

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethio-
4 methyl)succinyl]-L-phenylalanine-N-methylamide sodium
5 salt

6

7



10

11

12 [4-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethiomethyl)
13 succinyl]-L-phenylalanine-N-methylamide (0,2g, 0.4
14 mmol) was dissolved in 20ml of methanol and 1eq of 0.1N
15 NaOH(aq) added. The solvent was removed in vacuo and
16 the residue dissolved in water and freeze-dried
17 (0.21g, 0.4 mmol, 100%).

18

19 m.p. 170°C

20

21 [alpha]_D = -67° (c=1, methanol)

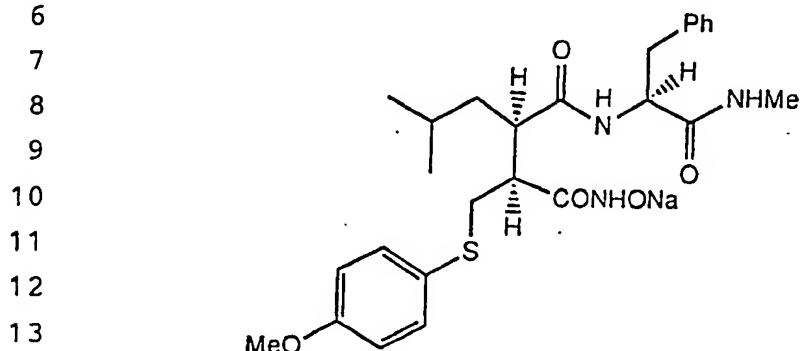
22

23 δ_H (250MHz, d₆-DMSO), 7.51 (1H, d), 7.19 - 6.97
24 (8H, m, aromatic H), 4.32 (1H, m, CHCH₂Ph), 3.00 (1H,
25 dd, J = 14,4Hz, CHCH₂Ph), 2.84 (1H, dd, J = 14,10Hz,
26 CHCH₂Ph) 2.53 (3H, d, J = 4.5Hz, NHCH₃), 2.46 2.19 (3H,
27 m), 1.37 (1H, m), 1.09 (1H, m), 0.93 (1H, m), and 0.67
28 (6H, m)

29

1 Example 12

2
 3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-
 4 thiomethyl)succinyl]-L-phenylalanine-N-methylamide
 5 sodium salt



17 [4-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenylthio-
 18 methyl)succinyl]-L-phenylalanine-N-methylamide (0.1g,
 19 0.2 mmol) was dissolved in 20ml of methanol and 1eq of
 20 0.1N NaOH(aq) added. The solvent was removed in vacuo
 21 and the residue dissolved in water and freeze-dried
 22 (0.1g, 0.2 mmol, 100%).

23
 24 m.p. 174°C

25
 26 $[\alpha]_D = -58^\circ$ (c=1, methanol)

27
 28 δ_H (250MHz, D_6 -DMSO) 7.26 - 7.04 (10H, m, aromatic
 29 H), 4.31 (1H, m, $CHCH_2Ph$), 3.73 (3H, s, OCH_3), 3.25 -
 30 2.72 (2H, m, $CHCH_2Ph$), 2.50 (3H, s, $NHCH_3$), 2.36 (1H,
 31 m), 2.15 (1H, m), 1.37 (1H, m), 0.95 (1H, m), and 0.69
 32 (6H, d, $CHCH_2(CH_3)_2$).

33

1 Example 13

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tertbutylphenyl-
4 thiomethyl) succinyl]-L-phenylalanine-N-methylamide

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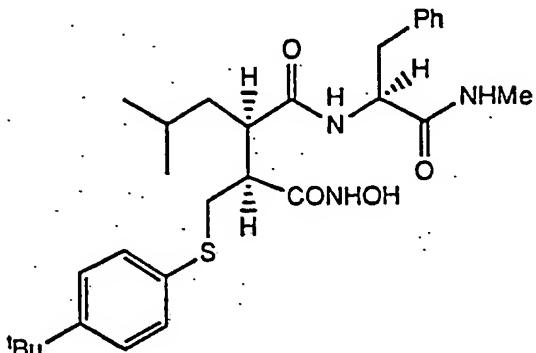
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33



[4-Hydroxy-2R-isobutyl-3S-(4-tertbutylphenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide (5.0g, 10 mmol) and HOBT (1.76g, 12 mmol) were dissolved in 1:1 DCM/DMF and the mixture cooled to 0°C before adding WSCl (2.3g, 12mmol) and NMM (1.2g, 12mmol). The mixture was stirred at 0°C for 1h to ensure complete formation of the activated ester. Hydroxylamine hydrochloride (1.0g, 15mmol) and NMM (1.2g, 15mmol) were dissolved in DMF then this mixture was added dropwise to the cooled solution of the activated ester. After 1h the reaction was poured into ether/water (1:1) whereupon the desired product precipitated as white crystals. These were collected by filtration, further washed with ether and water, then dried under vacuum at 50°C. This material was repeatedly recrystallised from methanol/water (1:1) to remove a trace of the minor diastereomer (0.7g, 1.3mmol, 14%).

1 M.p. 188.5 -190°C

2

3 Analysis calculated for C₂₉H₄₁N₃O₄S

4 Requires: C66.00 H7.83 N7.96

5 Found: C65.80 H7.81 N7.76

6

7 δ_H (250MHz, D₆-DMSO) 8.83 (1H, s, NHOH), 8.33 (1H,
8 d, J = 8Hz, CONH), 7.86 (1H, d, J = 6Hz, CONHMe), 7.28
9 - 6.90 (9H, m, aromatic H), 4.60 (1H, m, CHCH₂Ph), 2.94
10 (1H, dd, J = 14,4Hz, CHCH₂Ph), 2.77 (1H, dd, J =
11 14,10Hz, CHCH₂Ph), 2.58 (3H, d, J = 4.5Hz, NHCH₃), 2.55
12 - 2.37 (2H, m), 2.22 - 2.08 (2H, m, CH₂CH(CH₃)₂), 1.37
13 (2H, m), 1.26 (9H, s, C(CH₃)₃), 0.88 (1H, m,
14 CH₂CH(CH₃)₂), 0.81 (3H, d, J = 6Hz, CH(CH₃)₂), and 0.74
15 (3H, d, J = 6Hz, CH(CH₃)₂).

16

17 δ_C (63.9MHz, D₆-DMSO) 172.88, 171.59, 168.34,
18 147.87, 138.10, 133.09, 129.13, 127.95, 127.45, 126.36,
19 125.70, 54.19, 54.20, 46.38, 46.06, 37.70, 34.20, 32.79
20 31.24, 25.64, 25.19, 24.25, and 21.72.

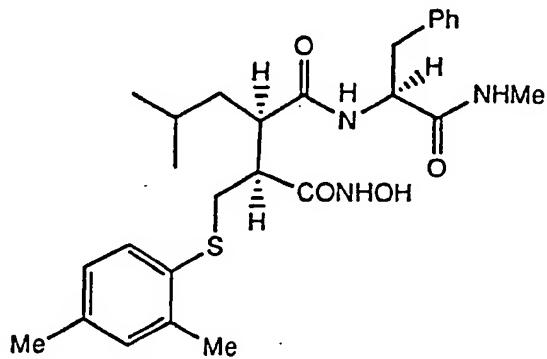
21

22 Example 14

23

24 [4 - (N - Hydroxyamino) - 2R - isobutyl - 3S - (2 , 4 -
25 dimethylphenylthiomethyl) succinyl] - L - phenylalanine - N -
26 methyleamide

27



1 [4-Hydroxy-2R-isobutyl-3S-(2,4-dimethylphenylthio-
2 methyl)succinyl]-L-phenylalanine-N-methylamide (1.8g,
3 3.7 mmol) and HOBT (0.67g, 12 mmol) were dissolved in
4 1:1 DCM/DMF and the mixture cooled to 0°C before adding
5 WSCl (0.86g, 4.5mmol) and NMM (0.45g, 4.5mmol). The
6 mixture was stirred at 0°C for 1h to ensure complete
7 formation of the activated ester. Hydroxylamine
8 hydrochloride (0.39g, 5.6mmol) and NMM (0.56g, 5.6mmol)
9 were dissolved in DMF then this mixture was added
10 dropwise to the cooled solution of the activated ester.
11 After 1h the reaction was poured into ether/water (1:1)
12 whereupon the desired product precipitated as white
13 crystals. These were collected by filtration, further
14 washed with ether and water, then dried under vacuum at
15 50°C. This material was repeatedly recrystallised from
16 methanol/water (1:1) to remove a trace of the minor
17 diastereomer (1.08g, 2.2mmol, 58%).
18

19 m.p. 226°C (dec.)
20

21 Analysis calculated for C₂₇H₃₇N₃O₄S

22 Requires: C64.90 H7.46 N8.41

23 Found: C65.15 H7.48 N8.40

24
25 δ_H (250MHz, D₆-DMSO) 8.83 (1H, s, NHOH), 8.32 (1H,
26 d, J = 8Hz, CONH), 7.85 (1H, d, J = 6Hz, CONHMe), 7.30
27 - 6.71 (9H, m, aromatic H), 4.56 (1H, m, CHCH₂Ph), 2.91
28 (1H, dd, J = 14,4Hz, CHCH₂Ph), 2.76 (1H, dd, J =
29 14,10Hz, CHCH₂Ph), 2.57 (3H, d, J = 4.5Hz, NHCH₃), 2.53
30 - 2.38 (2H, m), 2.23 (3H, s, C₆H₅(CH₃)₂), 2.13 (3H, s,
31 C₆H₅(CH₃), 1.30 (2H, m), 0.89 (1H, m, CH₂CH(CH₃)₂),
32 0.81 (3H, d, J = 6Hz, CH(CH₃)₂), and 0.74 (3H, d, J =
33 6Hz, CH(CH₃)₂).

1 Example 15

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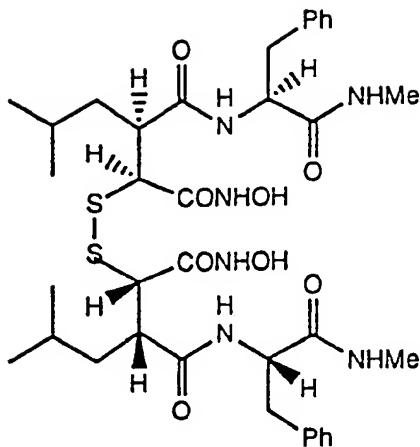
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12



13 [4-(N-Hydroxyamino-2R-isobutyl-3S-(acetylthiomethyl)
 14 succinyl]-L-phenylalanine-N-methylamide (1.0g, 2.4
 15 mmol) was dissolved in 750ml methanol and 350ml pH 7
 16 buffer added. Left to stand overnight and solvent
 17 removed in vacuo to 2/3 volume, left to crystallise for
 18 a further two hours. Filtered and dried to give 0.87g
 19 off-white crystals

20

21 Analysis calculated for $C_{38}H_{56}N_6O_8S_2 \cdot 1.9H_2O$

22 Requires: C55.34 H6.93 N9.88

23 Found: C55.44 H7.32 N10.21

24

25 Example 16

26

27 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenyl-
 28 thiomethyl) succinyl]-L-phenylalanine-N-methylamide

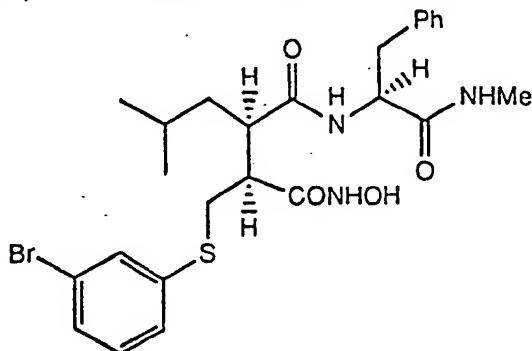
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32

33



1 Prepared by the method described in example 1g to give
2 material with the following characteristics.

3

4 m.p. 225 -229°C

5

6 $[\alpha]_D = -164.8^\circ$

7

8 Analysis calculated for $C_2^5H_{32}BrN_3O_4S$

9 Requires: C54.40 H5.89 N7.40

10 Found: C54.54 H5.86 N7.63

11

12 δ_H (250MHz, D_6 -DMSO) 8.83 (1H, s, $NHOH$), 8.35 (1H,
13 d, $J = 8Hz$, $CONH$), 7.90 (1H, q, $J = 6Hz$, $CONHMe$), 7.35
14 - 6.87 (9H, m, aromatic H), 4.64 (1H, m, $CHCH_2Ph$), 2.94
15 (1H, dd, $J = 14, 4Hz$, $CHCH_2Ph$), 2.76 (1H, t, $J = 13Hz$,
16 $CHCH_2Ph$) 2.60 (3H, d, $J = 5Hz$, $NHCH_3$), 2.55 - 2.35 (2H,
17 m, CH_2S), 2.15 (1H, t, $J = 10Hz$, $CHCO$), 2.01 (1H, d, J
18 = 11.5Hz, $CHCO$), 1.37 (2H, m), 0.88 (1H, m,
19 $CH_2CH(CH_3)_2$), 0.81 (3H, d, $J = 6Hz$, $CH(CH_3)_2$), and 0.74
20 (3H, d, $J = 6Hz$, $CH(CH_3)_2$).

21

22 δ_C (63.9MHz, D_6 -DMSO) 173.0, 171.0, 168.8, 139.8,
23 138.0, 130.5, 129.0, 128.5, 127.5, 125.8, 125.5, 54.2,
24 46.0, 45.5, 38.0, 31.5, 25.5, 25.2, 24.7, and 21.0.

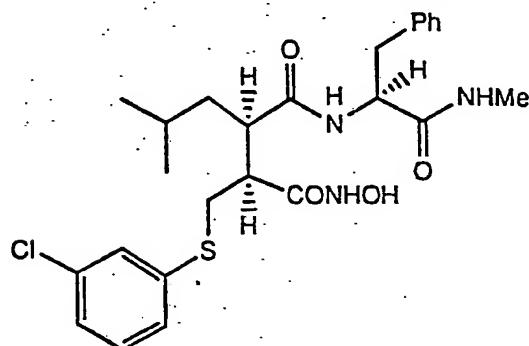
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26 Example 17

27

28 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthio-
29 methyl) succinyl]-L-phenylalanine-N-methylamide

30



1 Prepared by the method described in example 1g to give
2 material with the following characteristics.

3

4 m.p. 231-234°C

5

6 $[\alpha]_D = -96.5^\circ$

7

8 Analysis calculated for $C_2^5H_3^5ClN_3O_4S$

9 Requires: C59.34 H6.37 N8.30

10 Found: C59.51 H6.43 N8.24

11

12 δ_H (250MHz, D_6 -DMSO) 8.85 (1H, s, $NHOH$), 8.37 (1H,
13 d, $J = 8.5$ Hz, $CONH$), 7.90 (1H, m, $CONHMe$), 7.30 - 6.88
14 (9H, m, aromatic H), 4.66 (1H, m, $CHCH_2Ph$), 2.96 (1H,
15 bd, $J = 14$ Hz, $CHCH_2Ph$), 2.76 (1H, bt, $J = 13$ Hz,
16 $CHCH_2Ph$) 2.60 (3H, d, $J = 5$ Hz, $NHCH_3$), 2.55 - 2.40 (2H,
17 m, CH_2S), 2.16 (1H, m, $CHCO$), 2.01 (1H, d, $J = 14$ Hz,
18 $CHCO$), 1.37 (2H, m), 0.91 (1H, m, $CH_2CH(CH_3)_2$), 0.81
19 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$), and 0.74 (3H, d, $J =$
20 6Hz, $CH(CH_3)_2$).

21

22 δ_C (63.9MHz, D_6 -DMSO) 172.7, 171.6, 168.1, 139.2,
23 138.1, 130.3, 129.2, 127.9, 126.2, 125.9, 125.5, 125.0,
24 54.1, 46.3, 45.8, 37.8, 32.0, 25.7, 25.2, 24.2, and
25 21.7.

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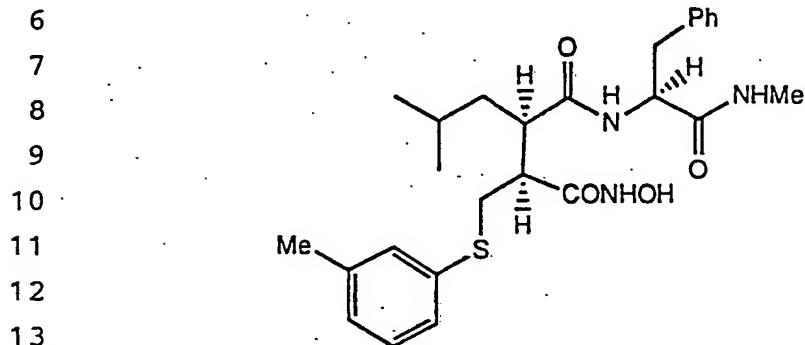
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1 Example 18

2

3 [4 - (N - H y d r o x y a m i n o) - 2 R - i s o b u t y l - 3 S - (3 -
4 m e t h y l p h e n y l t h i o m e t h y l) s u c c i n y l] - L - p h e n y l a l a n i n e - N -
5 m e t h y l a m i d e

1 Example 19

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-
4 aminophenylthiomethyl)succinyl]-L-phenylalanine-N-
5 methylamide.

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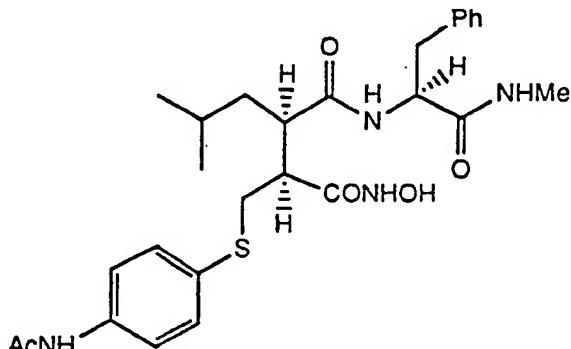
16

17 A) [2R-isobutyl-3S-(4-aminophenylthiomethyl)succinyl]-
18 L-phenylalanine -N-methylamide.

19

20 Prepared by the method described in example 1f to give
21 material with the following characteristics.

22

23 δ_H (250MHz, D_6 -DMSO) 8.27 (1H, d, $J = 8.5$ Hz, \underline{CONH}),
24 7.81 (1H, m, \underline{CONHMe}), 7.30 - 7.00 (5H, m, phenyl H),
25 6.86 (2H, d, $J = 8.5$ Hz, aromatic H), 6.45 (2H, d, $J =$
26 8.5Hz, aromatic H), 5.25 (1H, bs, $\underline{CO_2H}$), 4.48 (1H, m,
27 $\underline{CHCH_2Ph}$), 2.91 (1H, dd, $J = 14,4$ Hz, $\underline{CHCH_2Ph}$), 2.88 (1H,
28 dd, $J = 14,10$ Hz, $\underline{CHCH_2Ph}$) 2.56 (3H, d, $J = 5$ Hz, $\underline{NHCH_3}$),
29 2.43 - 2.24 (3H, m, $\underline{CH_2S}$ and \underline{CHCO}), 2.03 (1H, d, $J =$
30 10Hz, \underline{CHCO}), 1.41 (1H, t, $J = 11$ Hz, $\underline{CH_2CH(CH_3)_2}$), 1.26
31 (1H, m, $\underline{CH_2CH(CH_3)_2}$), 0.85 (1H, m, $\underline{CH_2CH(CH_3)_2}$), 0.81
32 (3H, d, $J = 6$ Hz, $\underline{CH(CH_3)_2}$), and 0.74 (3H, d, $J=6$ Hz,
33 $\underline{CH(CH_3)_2}$).

1 B) [2R-isobutyl-3S-(4-(N-acetyl)aminophenyl-thio-
2 methyl)- succinyl]-Lphenylalanine-N-methylamide.

3
4 The product from above (350mg, 0.74 mmol) was dissolved
5 in DCM (5 ml) cooled in an ice bath then triethylamine
6 (75mg, 0.74 mmol), DMAP (91mg, 7.4 mmol) and finally
7 acetic anhydride (83mg, 8.2 mmol) were added and the
8 solution stirred at RT for 90 minutes. The mixture was
9 partitioned between ethyl acetate and citric acid then
10 the organic layer washed with water and finally dried
11 over magnesium sulphate. Solvent removal gave the crude
12 product as pale yellow crystals (160mg, 0.31 mmol,
13 42%).

14
15 δ_H (250MHz, D_6 -DMSO) 9.94 (1H, s, CO_2H), 8.34 (1H,
16 d, $J = 8.5$ Hz, $CONH$), 7.90 (1H, m, $CONHMe$), 7.46 (2H, d,
17 $J = 8.5$ Hz, aromatic H) 7.30 - 7.00 (5H, m, phenyl H),
18 6.96 (2H, d, $J = 8.5$ Hz, aromatic H), 4.57 (1H, m,
19 $CHCH_2Ph$), 2.91 (1H, dd, $J = 14,4$ Hz, $CHCH_2Ph$), 2.88 (1H,
20 bt, $J = 13$ Hz, $CHCH_2Ph$), 2.58 (3H, d, $J = 5$ Hz, $NHCH_3$),
21 2.43 - 2.16 (3H, m, CH_2S and $CHCO$), 2.10 (1H, d, $J =$
22 14Hz, $CHCO$), 1.35 (1H, t, $J = 14$ Hz, $CH_2CH(CH_3)_2$), 1.26
23 (1H, m, $CH_2CH(CH_3)_2$), 0.86 (1H, m, $CH_2CH(CH_3)_2$), 0.81
24 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$), and 0.74 (3H, d, $J =$
25 6Hz, $CH(CH_3)_2$).

26
27 C) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-
28 aminophenylthiomethyl)succinyl]-L-phenylalanine-N-
29 methylamide.

30
31 Prepared by the method described in example 1g to give
32 material with the following characteristics.

33

1 m.p. 201 -202°C (dec.)

2

3 $[\alpha]_D = -7.5^\circ$ (c=1.0, methanol)

4

5 δ_H (250MHz, D_6 -DMSO) 9.90 (1H, s, NHOH), 8.82 (1H,
6 s, NHOH), 8.30 (1H, d, $J = 8.5$ Hz, CONH), 7.85 (1H, m,
7 CONHMe), 7.45 (2H, d, $J = 8.5$ Hz, aromatic H), 7.28 -
8 6.94 (5H, m, phenyl H), 6.90 (2H, d, $J = 8.5$ Hz,
9 aromatic H), 4.66 (1H, m, CHCH_2Ph), 2.90 (1H, dd, $J =$
10 14,4Hz, CHCH_2Ph), 2.76 (1H, bt, $J = 13$ Hz, CHCH_2Ph),
11 2.50 (3H, d, $J = 5$ Hz, NHCH_3), 2.49 - 2.35 (2H, m,
12 CH_2S), 2.14 (1H, m, CHCO), 2.03 (4H, s + m, COCH_3 and
13 CHCO), 1.35 (2H, m), 0.86 (1H, m, CH_2CH(CH_3)_2), 0.81
14 (3H, d, $J = 6$ Hz, CH(CH_3)_2), and 0.74 (3H, d, $J = 6$ Hz,
15 CH(CH_3)_2).

16

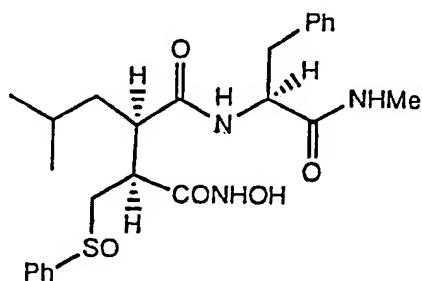
17 Example 20

18

19 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfinyl-
20 methylsuccinyl]-L-phenylalanine-N-methylamide.

21

22



23

24

25

26

27

28

29

30

31 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-
32 succinyl]-L-phenylalanine-N-methylamide (250mg,
33 0.53mmol) was dissolved in methanol (50 ml) and meta-

1 chloroperbenzoic acid (100mg, 0.58 mmol) was added.
2 After stirring for 1h at room temperature ether was
3 added and the mixture filtered. Solvent removal gave
4 the crude white solid which was recrystallised from
5 methanol / water then slurried in ether to remove final
6 traces of meta-chlorobenzoic acid to give the desired
7 material (70 mg, 0.014 mmol, 27%).

8

9 m.p. 186 -188°C

10

11 $[\alpha]_D = -13.6^\circ$ (c=0.5, methanol)

12

13 Analysis calculated for $C_{25}H_{33}N_3O_5S \cdot 0.5H_2O$

14 Requires: C60.46 H6.90 N8.46

15 Found: C60.58 H6.69 N8.29

16

17 δ_H (250MHz, D_6 -DMSO, mixture of diastereomers) 9.04
18 + 8.93 (1H, 2xs, NHOH), 8.29 + 8.16 (1H, 2xd, $J = 8.5$
19 Hz, CONH), 7.79 (1H, m, CONHMe), 7.90 - 7.40 (8H, m,
20 aromatic H), 7.06 + 6.82 (2H, 2xm, SO-Aromatic), 4.37
21 (1H, m, CHCH_2Ph), 2.93 - 2.58 (3H, m, containing
22 CHCH_2Ph), 2.52 (3H, m, NHCH_3), 2.49 + 2.37 (1H, 2xm),
23 1.49 - 1.25 (2H, m, CH_2CH(CH_3)_2 and CH_2CH(CH_3)_2), 0.95
24 (1H, m, CH_2CH(CH_3)_2), 0.81 (3H, d, $J = 6$ Hz, CH(CH_3)_2),
25 and 0.74 (3H, d, $J=6$ Hz, CH(CH_3)_2).

26

27 δ_C (63.9MHz, D_6 -DMSO, mixture of diastereomers)
28 172.2, 171.4, 171.3, 167.7, 144.5, 138.0, 137.9, 131.3,
29 130.9, 129.6, 129.3, 129.1, 128.8, 128.3, 127.8, 126.5,
30 126.2, 124.3, 123.6, 59.8, 58.1, 54.3, 54.0, 46.2,
31 45.8, 41.6, 40.9, 37.6, 37.4, 25.6, 25.0, 24.3, 24.2,
32 21.7, and 21.6.

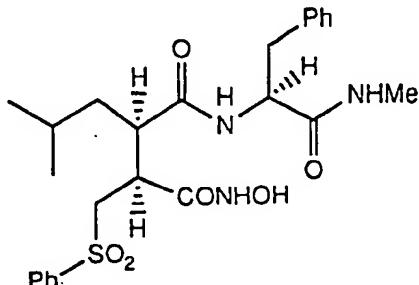
33

1 Example 21

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-
4 methylsuccinyl]-L-phenylalanine-N-methylamide.

5



6

7

8 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-
9 succinyl]-L-phenylalanine-N-methylamide (50mg,
10 0.11mmol) was dissolved in methanol (12 ml) and meta-
11 chloroperbenzoic acid (40mg, 0.23 mmol) was added.
12 After stirring for 3h at room temperature ether was
13 added and the mixture filtered. Solvent removal gave
14 the crude white solid which was slurried in ether to
15 remove final traces of meta-chlorobenzoic acid to give
16 the desired material.

17

18 m.p. 228 - 231°C

19

20 [alpha]_D = 16.8° (c=0.5, methanol)

21

22 Analysis calculated for C₂₅H₃₃N₃O₆S·0.3H₂O

23 Requires: C58.99 H6.65 N8.25

24 Found: C58.92 H6.51 N8.05

25

26 delta_H (250MHz, D₆-DMSO) 8.66 (1H, s, NH_{OH}), 8.25 (1H,
27 d, J = 8.5 Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50
28 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H),

1 4.36 (1H, m, CHCH_2Ph), 2.86 (1H, dd, $J = 14,5$ Hz,
 2 CHCH_2Ph), 2.75 (1H, dd, $J = 14,10$ Hz, CHCH_2Ph), 2.54
 3 (3H, d, $J = 4.5$ Hz, NHCH_3), 2.54 (2H, m), 1.30 (2H, m,
 4 $\text{CH}_2\text{CH}(\text{CH}_3)_2$ and $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.86 (1H, m,
 5 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71
 6 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$).

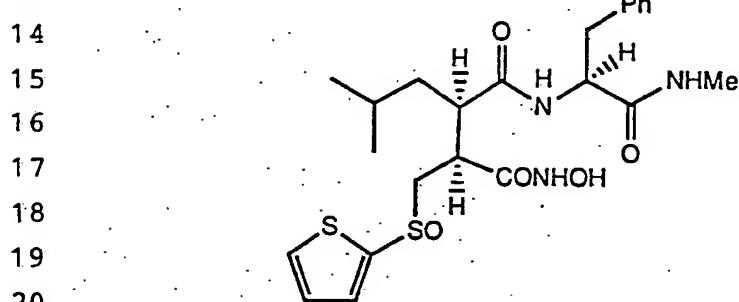
7

8 Example 22

9

10 [4 - (N - Hydroxyamino) - 2R - isobutyl - 3S -
 11 thiophenylsulphinylmethyl-succinyl] -L-phenylalanine-N-
 12 methylamide

13



22 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylthio-
 23 methyl-succinyl]-L-phenylalanine-N-methylamide (50mg,
 24 0.11mmol) was treated as described in example 21 to
 25 yield the title compound (16mg, 0.03 mmol, 29%) as a
 26 mixture of diastereomer with the following
 27 characteristics:

28

29 m.p. 195 -197°C (dec.)

30

31 Analysis calculated for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_5\text{S}_2 \cdot 0.5\text{H}_2\text{O}$

32 Requires: C54.96 H6.42 N8.36

33 Found: C54.91 H6.23 N8.23

1 delta_H (250MHz, D₆-DMSO, mixture of diastereomers) 9.04
2 + 8.96 (1H, 2xs, NH_{OH}), 8.34 + 8.29 (1H, 2xd, J = 8.5
3 Hz, CONH), 8.02 + 7.98 (1H, 2xm, CONHMe), 7.81 (1H, bs,
4 thiophene-H), 7.42 (1H, s, thiophene-H), 7.25 - 7.15
5 (5H, m, phenyl), 7.03 (1H, bs, thiophene-H), 4.43 (1H,
6 m, CHCH₂Ph), 3.0 - 2.6 (4H, m, containing CHCH₂Ph),
7 2.52 (7H, m, containing NHCH₃), 2.05 (1H, m), 1.6 - 1.2
8 (2H, m, CH₂CH(CH₃)₂ and CH₂CH(CH₃)₂), 0.87 (1H, m,
9 CH₂CH(CH₃)₂), and 0.85 - 0.71 (6H, m, CH(CH₃)₂).

10

11 Example 23

12

13 [4 - (N - H y d r o x y a m i n o) - 2 R - i s o b u t y l - 3 S -
14 t h i o p h e n y l s u l p h o n y l m e t h y l - s u c c i n y l] - L - p h e n y l a l a n i n e - N -
15 m e t h y l a m i d e .

16

17

18

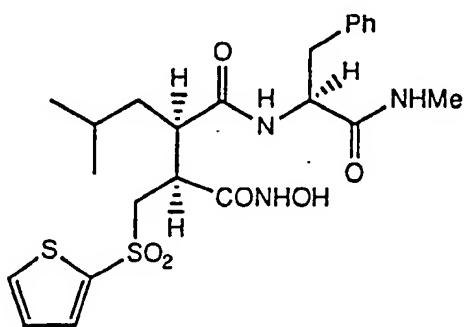
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20

21

22

23



24

25 [4 - (N - H y d r o x y a m i n o) - 2 R - i s o b u t y l - 3 S - t h i o p h e n y l t h i o -
26 m e t h y l - s u c c i n y l] - L - p h e n y l a l a n i n e - N - m e t h y l a m i d e (75 m g ,
27 0.16 m m o l) w a s t r e a t e d a s d e s c r i b e d i n e x a m p l e 22 t o
28 y i e l d t h e t i t l e c o m p o u n d (40 m g , 0.08 m m o l , 49 %) w i t h
29 t h e f o l l o w i n g c h a r a c t e r i s t i c s :

30

31 m.p. 215 - 216°C

32

33 Analysis calculated for C₂₃H₃₁N₃O₆S₂

1 Requires: C54.21 H6.13 N8.24

2 Found: C54.07 H6.19 N8.04

3

4 δ_H (250MHz, D_6 -DMSO) 887 (1H, s, NHOH), 8.25 (1H,
 5 d, J = 8.5 Hz, CONH), 8.09 (1H, d, J = 4.7 Hz,
 6 thiophene-H), 7.83 (1H, m, CONHMe), 7.53 (1H, d, J = 3.
 7 Hz, thiophene H), 7.25 - 7.12 (6H, m, phenyl and
 8 thiophene-H), 4.36 (1H, m, CHCH_2Ph), 3.38 (1H, dd, J =
 9 14,11 Hz, SCH_2), 2.87 (1H, dd, J = 14,5 Hz, CHCH_2Ph),
 10 2.75 (1H, dd, J = 14,10 Hz, CHCH_2Ph), 2.70 - 2.36 (6H,
 11 m, containing NHCH_3), 1.20 (2H, m, CH_2CH(CH_3)_2 and
 12 CH_2CH(CH_3)_2), 0.89 (1H, m, CH_2CH(CH_3)_2), and 0.75 (6H,
 13 m, CH(CH_3)_2).

14

15 $\delta_{^13C}$ (63.9MHz, D_6 -DMSO) 172.0, 171.2, 166.5, 140.0,
 16 138.0, 135.4, 134.6, 129.0, 128.4, 128.2, 126.6, 54.3,
 17 45.6, 37.5, 25.6, 25.0, 24.2, and 21.7.

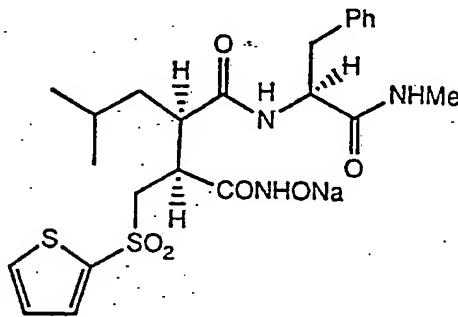
18

19 Example 24

20

21 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-
 22 methylsuccinyl]-L-phenylalanine-N-methylamide sodium
 23 salt.

24

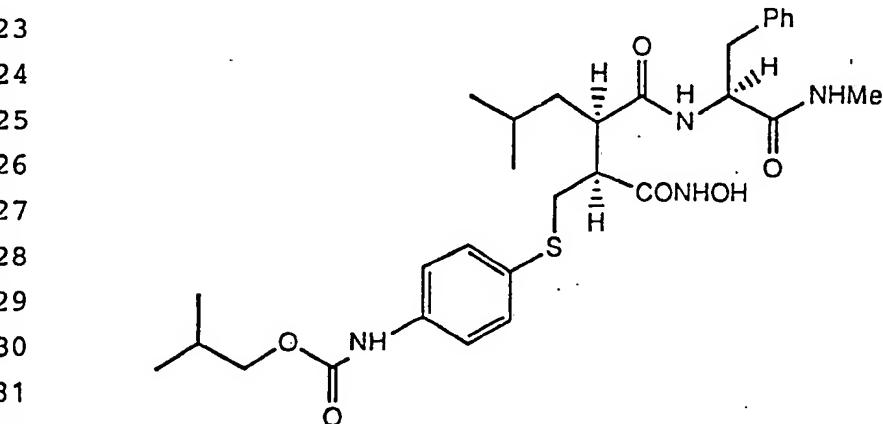


1 methylsuccinyl]-L-phenylalanine-N-methylamide (50mg,
 2 0.1mmol) was dissolved in methanol (10ml) and sodium
 3 hydroxide solution (0.1M, 1.0ml) added to give a
 4 homogeneous solution. The methanol was removed under
 5 reduced pressure then the residual aqueous solution
 6 freeze dried to give the title compound (40mg).

7
 8 δ_H (250MHz, D_6 -DMSO) 8.66 (1H, s, NH_{OH}), 8.25 (1H,
 9 d, J = 8.5 Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50
 10 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H),
 11 4.36 (1H, m, CHCH₂Ph), 2.86 (1H, dd, J = 14,5 Hz,
 12 CHCH₂Ph), 2.75 (1H, dd, J = 14,10 Hz, CHCH₂Ph), 2.54
 13 (3H, d, J=4.5 Hz, NHCH₃), 2.54 (2H, m), 1.30 (2H, m,
 14 CH₂CH(CH₃)₂ and CH₂CH(CH₃)₂), 0.86 (1H, m,
 15 CH₂CH(CH₃)₂), 0.75 (3H, d, J = 6Hz, CH(CH₃)₂), and 0.71
 16 (3H, d, J = 6Hz, CH(CH₃)₂).

17
 18 Example 25

19
 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutoxy-
 21 carbonylamino)phenyl)thiomethyl-succinyl]-L-phenyl-
 22 alanine-N-methylamide



1 methylsuccinyl]-L-phenylalanine-N-methylamide was
2 prepared by the method described in example 1f to give
3 a compound with the following characteristics.

4
5 δ_{H} (250MHz, D_6 -DMSO) 8.26 (1H, d, J = 8.5 Hz,
6 CONH), 7.81 (1H, m, CONHMe), 7.27 - 7.15 (5H, m, phenyl
7 H), 6.85 (2H, d, J = 8.5Hz, aromatic H), 6.46 (2H, d, J
8 = 8.5Hz, aromatic H), 5.2 (1H, bs, CO_2H), 4.48 (1H, m,
9 CHCH_2Ph), 2.90 (1H, dd, J = 13.5, 4.3 Hz, CHCH_2Ph), 2.75
10 (1H, dd, J = 13.6, 10 Hz, CHCH_2Ph), 2.56 (3H, d, J =
11 4.5 Hz, NHCH₃), 2.50 - 2.25 (3H, m), 2.03 (1H, d, J =
12 10 Hz), 1.41 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.26 (1H, m,
13 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.86 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, J
14 = 6Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71 (3H, d, J = 6Hz, $\text{CH}(\text{CH}_3)_2$).

15
16 b) N,N-Dimethylglycine (100mg, 0.97 mmol) was stirred
17 in dry THF (50ml) and triethylamine (108mg, 1.1mmol)
18 and isobutylchloroformate (146mg, 1.1mmol) were added.
19 After 1h the product from example 26a (500mg, 1.1mmol)
20 was added and the mixture stirred for a further 1h. The
21 reaction was worked up by partitioning between citric
22 acid and ethyl acetate, drying the organic layer and
23 solvent removal to give the crude product (1g).
24 Solution of the crude solid in ethyl acetate then
25 precipitation with ether resulted in white crystals of
26 the isobutylchloroformate derivative.

27
28 c) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-
29 carbonylamino) phenyl)thiomethyl-succinyl]-L-phenyl-
30 alanine-N-methylamide

31
32 The product from example 26b was converted to the
33 hydroxamic acid as described in example 1g. to give a
compound with the following characteristics.

1 m.p. 198 - 200°C

2

3 $[\alpha]_D = -8.5^\circ$ (c=1, methanol)

4

5 Analysis calculated for $C_{30}H_{42}N_4O_6S$

6 Requires: C61.41 H7.22 N9.55

7 Found: C62.04 H7.32 N9.67

8

9 δ_{H} (250MHz, D_6 -DMSO) 9.60 (1H, s, NHOH), 8.83 (1H, s, NHOH), 8.31 (1H, d, $J = 8.5$ Hz, CONH), 7.85 (1H, m, CONHMe), 7.36 - 7.25 (4H, m, aromatic H), 7.14 - 7.05 (3H, m, aromatic H), 6.91 (2H, d, $J = 8.5$ Hz, aromatic H), 4.56 (1H, m, CHCH_2Ph), 3.87 (2H, d, $J = 7$ Hz, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 2.92 (1H, dd, $J = 13.7, 4.0$ Hz, CHCH_2Ph), 2.76 (1H, dd, $J = 13.6, 10$ Hz, CHCH_2Ph), 2.58 (3H, d, $J = 4.5$ Hz, NHCH_3), 2.50 - 2.34 (2H, m), 2.16 - 1.87 (3H, m), 1.35 (2H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$ and $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.93 (6H, d, $J = 6.6$ Hz, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 0.87 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$).

21

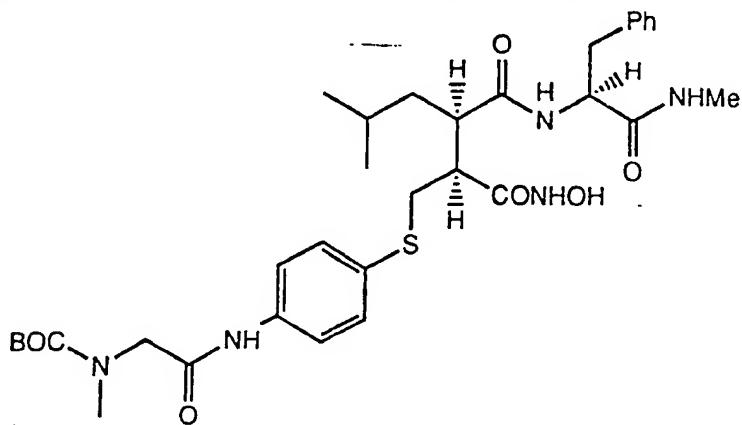
22

23 Example 26

24

25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-
26 (tertbutoxycarbonyl)-glycylamino) phenyl)thiomethyl-
27 succinyl]-Lphenylalanine-N-methylamide.

28



1 a) [4-Hydroxy-2R-isobutyl-3S-(4-(N-methyl-N-(tert-
2 butoxycarbonyl)glycylamino) phenyl)thiomethyl-
3 succinyl]-L-phenylalanine-N-methylamide was prepared as
4 described in example 26b by substitution of N-BOC
5 sarcosine for the acid component.

6
7 δ_H (250MHz, D_6 -DMSO) 9.97 (1H, s, CO_2H), 8.36 (1H,
8 d, $J = 8.5$ Hz, $CONH$), 7.91 (1H, m, $CONHMe$), 7.48 (2H,
9 d, $J = 8.5$ Hz, aromatic H), 7.40 - 7.05 (5H, m, aromatic
10 H), 6.97 (2H, d, $J = 8.5$ Hz, aromatic H), 4.58 (1H, m,
11 $CHCH_2Ph$), 3.95 (2H, d, $J = 9$ Hz, NCH_2CO), 2.92 (4H, m+d,
12 $CHCH_2Ph$ and $BOCNCH_3$), 2.76 (1H, dd, $J = 13, 10$ Hz,
13 $CHCH_2Ph$), 2.58 (3H, d, $J = 4.5$ Hz, $NHCH_3$), 2.50 - 2.09
14 (4H, m), 1.46 - 1.33 (11H, m + 2xs, $(CH_3)_3C$,
15 $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.87 (1H, m,
16 $CH_2CH(CH_3)_2$), 0.75 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$), and
17 0.71 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$).

18 b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl- N-
19 (tertbutoxycarbonyl)-glycylamino)phenyl)- thiomethyl-
20 succinyl]-Lphenylalanine-N-methylamide was prepared
21 from the material produced in example 27a as described
22 in example 1g.

24
25 δ_H (250MHz, D_6 -DMSO) 9.97 (1H, s, $CONHOH$), 8.83
26 (1H, s, $NHOH$), 8.32 (1H, d, $J = 8.5$ Hz, $CONH$), 7.86
27 (1H, m, $CONHMe$), 7.46 (2H, d, $J = 8.5$ Hz, aromatic H),
28 7.28 - 7.00 (5H, m, aromatic H), 6.97 (2H, d, $J =$
29 8.5 Hz, aromatic H), 4.56 (1H, m, $CHCH_2Ph$), 3.94 (2H, d,
30 $J = 9$ Hz, NCH_2CO), 2.87 (4H, m+d, $CHCH_2Ph$ and $BOCNCH_3$),
31 2.76 (1H, m, $CHCH_2Ph$), 2.57 (3H, d, $J = 4.5$ Hz, $NHCH_3$),
32 2.25 - 1.91 (2H, m), 1.42 - 1.30 (11H, m + 2xs,
33 $(CH_3)_3C$, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.92 (1H, m,
 $CH_2CH(CH_3)_2$), 0.80 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$), and
0.73 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$).

1

2 Example 27

3

4 Collagenase inhibition activity

5

6 The potency of compounds of general formula I to act
7 as inhibitors of collagenase (a metalloproteas
8 involved in tissue degradation) was determined by the
9 procedure of Cawston and Barrett, (Anal. Biochem., 99,
10 340-345, 1979), hereby incorporated by reference,
11 whereby a 1mM solution of the inhibitor being tested or
12 dilutions thereof was incubated at 37° for 16 hours
13 with collagen and collagenase (buffered with 25mM
14 Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35 and
15 0.02% NaN₃). The collagen was acetylated ¹⁴C collagen
16 prepared by the method of Cawston and Murphy (Methods
17 in Enzymology, 80, 711, 1981), hereby incorporated by
18 reference. The samples were centrifuged to sediment
19 undigested collagen and an aliquot of the radioactive
20 supernatant removed for assay on a scintillation
21 counter as a measure of hydrolysis. The collagenase
22 activity in the presence of 1 mM inhibitor, or a
23 dilution thereof, was compared to activity in a control
24 devoid of inhibitor and the results reported below as
25 that inhibitor concentration effecting 50% inhibition
26 of the collagenase (IC₅₀).

27

28	<u>Compound of Example No.</u>	<u>IC₅₀</u>
29	1	20 nM
30	2	8 nM
31	5	3 nM
32	6	(50% @ 1 μM)
33		

1
2 Example 28
3

4 **Stromelysin inhibition activity**
5

6 The potency of compounds of general formula I to act as
7 inhibitors of stromelysin was determined using the
8 procedure of Cawston et al (Biochem. J., 195, 159-165
9 1981), hereby incorporated by reference, whereby a 1mM
10 solution of the inhibitor being tested or dilutions
11 thereof was incubated at 37°C for 16 hours with
12 stromelysin and ^{14}C acetylate casein (buffered with
13 25mM Hepes, pH 7.5 containing 5mM CaCl_2 , 0.05% Brij 35
14 and 0.02% NaN_3 . The casein was ^{14}C acetylated
15 according to the method described in Cawston et al
16 (Biochem. J., 195, 159-165, 1981), hereby incorporated
17 by reference. The stromelysin activity in the presence
18 of 1mM, or a dilution thereof, was compared to activity
19 in a control devoid of inhibitor and the results
20 reported below as that inhibitor concentration
21 effecting 50% inhibition of the stromelysin (IC_{50}).
22

23	<u>Compound of Example No.</u>	<u>IC_{50}</u>
24	1	10 nM
25	2	20 nM

26 Examples of unit dosage compositions are as follows:
27

28
29
30
31
32
33

1

2

3

4 Example 29

5

6 **Capsules:**

		Per 10,000
	<u>Ingredients</u>	<u>Per Capsule</u>
		<u>Capsules</u>
10	1. Active ingredient	
11	Cpd. of Form. I	40.0 mg
12	2. Lactose	150.0 mg
13	3. Magnesium	
14	stearate	<u>4.0 mg</u>
15		<u>40 g</u>
		194.0 mg
		1940 g

16

17 **Procedure for capsules:**

18

19 Step 1. Blend ingredients No. 1 and No. 2 in a
20 suitable blender.21 Step 2. Pass blend from Step 1 through a No. 30 mesh
22 (0.59 mm) screen.23 Step 3. Place screened blend from Step 2 in a
24 suitable blender with ingredient No. 3 and
25 blend until the mixture is lubricated.26 Step 4. Fill into No. 1 hard gelatin capsule shells
27 on a capsule machine.

28

29

30

31

32

33

1 Example 30

2

3 **Tablets:**

4			Per 10,000
5	<u>Ingredients</u>	<u>Per Tablet</u>	<u>Tablets</u>
6			
7	1. Active ingredient		
8	Cpd. of Form. I	40.0 mg	400 g
9	2. Corn Starch	20.0 mg	200 g
10	3. Alginic acid	20.0 mg	200 g
11	4. Sodium alginate	20.0 mg	200 g
12	5. Magnesium		
13	stearate	<u>1.3 mg</u>	<u>13 g</u>
14		101.3 mg	1013 g

15

16 **Procedure for tablets:**

17 Step 1. Blend ingredients No. 1, No. 2, No. 3 and No. 18 4 in a suitable mixer/blender.

19 Step 2. Add sufficient water portionwise to the blend 20 from Step 1 with careful mixing after each 21 addition. Such additions of water and mixing 22 until the mass is of a consistency to permit 23 its conversion to wet granules.

24 Step 3. The wet mass is converted to granules by 25 passing it through an oscillating granulator 26 using a No. 8 mesh (2.38) screen.

27 Step 4. The wet granules are then dried in an oven at 28 140°F (60°C) until dry.

29 Step 5. The dry granules are lubricated with 30 ingredient No. 5.

31 Step 6. The lubricated granules are compressed on a 32 suitable tablet press.

33

1 Example 31

2

3 **Intramuscular Injection:**

4	<u>Ingredient</u>	<u>Per ml.</u>	<u>Per liter</u>
5	1. Compound of Formula I		
6	Active ingredient	10.0 mg	10 g
7	2. Istonic buffer		
8	solution pH 4.0.	q.s.	q.s.

9

10 **Procedure:**

11 Step 1. Dissolve the active ingredient in the buffer
12 solution.

13 Step 2. Aseptically filter the solution from Step 1.

14 Step 3. The sterile solution is now aseptically
15 filled into sterile ampoules.

16 Step 4. The ampoules are sealed under aspetic
17 conditions.

18

19 Example 32

20

21 **Suppositories:**

22	<u>Per</u>		
23	<u>Ingredients</u>	<u>Per Supp.</u>	<u>1,000 Supp</u>
24	1. Compound of Form. I		
25	Active ingredient	40.0 mg	40 g
26	2. Polyethylene Glycol		
27	1000	1350.0 mg	1,350 g
28	3. Polyethylene Glycol		
29	4000	450.0 mg	450 g
30		1840.0 mg	1,840 g

31

32

33

1 **Procedure:**

2 Step 1. Melt ingredient No. 2 and No. 3 together and
3 stir until uniform.

4 Step 2. Dissolve ingredient No. 1 in the molten mass
5 from Step 1 and stir until uniform.

6 Step 3. Pour the molten mass from Step 2 into
7 suppository moulds and chill.

8 Step 4. Remove the suppositories from moulds and
9 wrap.

10

11 **Example 33**

12

13 **Eye Ointment**

14

15 An appropriate amount of a compound of general formula
16 I is formulated into an eye ointment base having the
17 following composition:

18

19	Liquid paraffin	10%
20	Wool fat	10%
21	Yellow soft paraffin	80%

22

23 **Example 34**

24

25 **Topical skin ointment.**

26

27 An appropriate amount of a compound of general formula
28 I is formulated into a topical skin ointment base
29 having the following composition:

30

31	Emulsifying wax	30%
32	White soft paraffin	50%
33	Liquid paraffin	20%

1 CLAIMS

2

3 1. A compound of general formula I:

4

5

6

7

8

9

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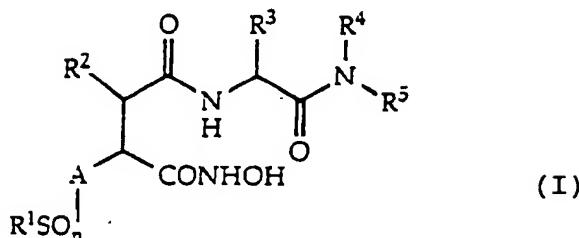
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32

33



11 wherein:

12

13 R¹ represents a C₁-C₆ alkyl, phenyl, thiophenyl,
 14 substituted phenyl, phenyl(C₁-C₆)alkyl,
 15 heterocyclyl, (C₁-C₆)alkylcarbonyl or phenacyl or
 16 substituted phenacyl group; or when n = 0, R¹
 17 represents SR^X, wherein R^X represents a group:

18

19

20

21

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26

27

28

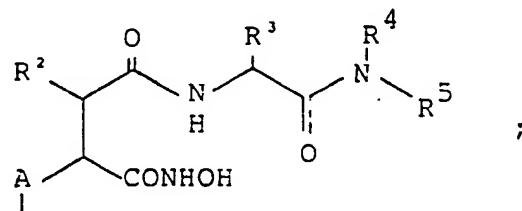
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30

31

32

33



26 R² represents a hydrogen atom or a C₁-C₆ alkyl, C₁-C₆
 27 alk en y l , p h e n y l (C₁ - C₆) a l k y l ,
 28 cycloalkyl(C₁-C₆)alkyl or cycloalkenyl(C₁-C₆)alkyl
 29 group;

30

31

32

33

31 R³ represents an amino acid side chain or a C₁-C₆
 32 alkyl, benzyl, (C₁-C₆ alkoxy)benzyl or
 33 benzyl oxy(C₁-C₆ alkyl) or benzyl oxy benzyl group;

1 R^4 represents a hydrogen atom or a C_1 - C_6 alkyl group;
2
3 R^5 represents a hydrogen atom or a methyl group;
4
5 n is an integer having the value 0, 1 or 2; and
6
7 A represents a C_1 - C_6 hydrocarbon chain, optionally
8 substituted with one or more C_1 - C_6 alkyl, phenyl
9 or substituted phenyl groups;
10
11 or a salt thereof.

12
13 2. A compound as claimed in Claim 1, in which the
14 chiral centre adjacent the substituent R^3 has S
15 stereochemistry.

16
17 3. A compound as claimed in Claim 1 or 2, wherein the
18 chiral centre adjacent the substituent R^2 has R
19 stereochemistry.

20
21 4. A compound as claimed in Claim 1, 2 or 3, in which
22 R^1 represents a hydrogen atom or a C_1 - C_4 alkyl, phenyl,
23 thiophenyl, benzyl, acetyl or phenacyl group.

24
25 5. A compound as claimed in any one of Claims 1 to 4,
26 wherein R^2 represents a C_3 - C_6 alkyl group.

27
28 6. A compound as claimed in any one of Claims 1 to 5,
29 wherein R^3 represents a benzyl or
30 4-(C_1 - C_6)alkoxyphenylmethyl or benzyloxybenzyl group.

31
32 7. A compound as claimed in any one of Claims 1 to 6,
33 wherein R^4 represents a C_1 - C_4 alkyl group.

1 8. A compound as claimed in any one of Claims 1 to 7,
2 wherein R⁵ represents a hydrogen atom.

3
4 9. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
5 methyl)-succinyl]-L-phenylalanine-N-methylamide,

6
7 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthio-
8 methyl) succinyl]-L-phenylalanine-N-methylamide,

9
10 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthiomethyl)
11 succinyl]-L-phenylalanine-N-methylamide,

12
13 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)
14 succinyl]-L-phenylalanine-N-methylamide or

15
16 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl)
17 succinyl]-L-phenylalanine-N-methylamide

18
19 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloylthiomethyl)
20 succinyl]-L-phenylalanine-N-methylamide

21
22 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)
23 succinyl]-L-phenylalanine-N-methylamide sodium salt

24
25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-
26 thiomethyl)succinyl]-L-phenylalanine-N-methylamide

27
28 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
29 thiomethyl)succinyl]-L-phenylalanine-N-methylamide

30
31 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethio-
32 methyl)succinyl]-L-phenylalanine-N-methylamide sodium
33 salt

- 1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide sodium salt
- 4
- 5 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tertbutylphenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 7
- 8 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-dimethylphenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 10
- 11 bis-S,S'-{[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethyl)succinyl]-L-phenylalanine-N-methylamide} disulphide
- 13
- 14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 16
- 17 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 19
- 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methylphenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 22
- 23 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-amino-phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide
- 26
- 27 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphinyl-methylsuccinyl]-L-phenylalanine-N-methylamide
- 29
- 30 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-methylsuccinyl]-L-phenylalanine-N-methylamide
- 32
- 33

1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphiny1-
2 methylsuccinyl]-L-phenylalanine-N-methylamide
3
4 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphonyl-
5 methylsuccinyl]-L-phenylalanine-N-methylamide
6
7 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-
8 methylsuccinyl]-L-phenylalanine-N-methylamide sodium
9 salt
10
11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-
12 carbonylamino)phenyl)thiomethylsuccinyl]-L-phenyl-
13 alanine-N-methylamide
14
15 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-
16 (tert-butoxycarbonyl)-glycylamino)phenyl)thiomethyl-
17 succinyl]-L-phenylalanine-N-methylamide
18
19 or, where appropriate, a salt of such a compound.
20
21 10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-
22 thiomethyl) succinyl]-L-phenylalanine-N-methylamide, or
23
24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiomethyl)
25 succinyl]-L-phenylalanine-N-methylamide
26
27 or a salt thereof.
28
29 11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-
30 thiomethyl)succinyl]-L-phenylalanine-N-methylamide or a
31 salt thereof.
32
33

1 12. A compound as claimed in any one of claims 1 to 11
 2 for use in human or veterinary medicine.

3

4 13. The use of a compound as claimed in any one of
 5 claims 1 to 11 in the preparation of an agent for use
 6 in the management of disease involving tissue
 7 degradation and/or in the promotion of wound healing.

8

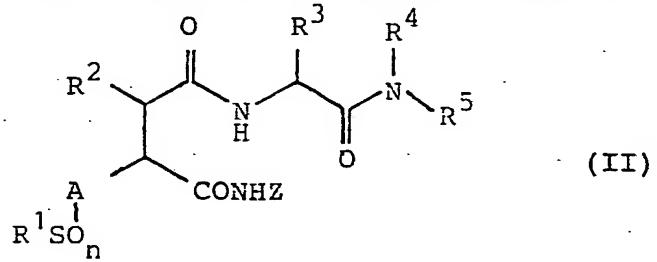
9 14. A pharmaceutical or veterinary formulation
 10 comprising a compound as claimed in any one of claims 1
 11 to 11 and a pharmaceutically and/or veterinarily
 12 acceptable carrier.

13

14 15. A process for preparing a compound of general
 15 formula I as defined in claim 1, the process
 16 comprising:

17

18 (a) deprotecting a compound of general formula II



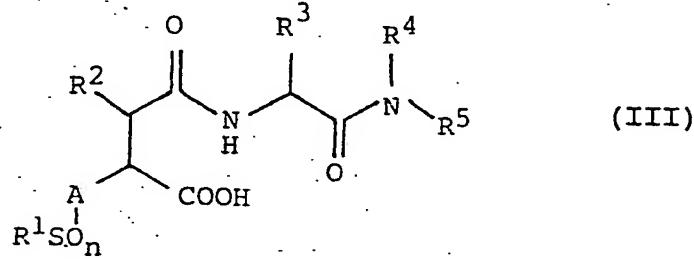
24 wherein: $\text{R}^1 \text{SO}_n$

25

26 R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
 27 general formula I and Bn represents a
 28 benzyloxycarbonyl group; or

29

30 (b) reacting a compound of general formula III



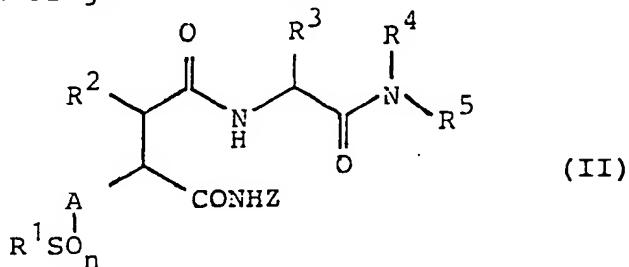
1 wherein:

2 R¹, R², R³, R⁴, R⁵, A and n are as defined in
3 general formula I,

6 with hydroxylamine or a salt thereof; and

8 (c) optionally after step (a) or step (b) converting a
9 compound of general formula I into another compound of
0 general formula I.

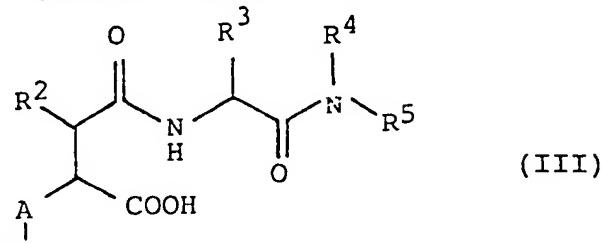
11
12 16. A compound of general formula II



18 wherein:

20 R^1, R^2, R^3, R^4, R^5 , A and n are as defined in
21 general formula I and Z represents a protecting
22 group.

24 17. A compound of general formula III.



30 wherein:

32 R^1, R^2, R^3, R^4, R^5 , A and n are as defined in
33 general formula I.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 89/01399

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁵ C 07 C 323/62, 323/60, C 07 D 333/34, C 07 C 327/32,
IPC : 317/50, 313/48, A 61 K 31/13, 31/38

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
IPC ⁵	C 07 C 259/00, 323/00, C 07 D 333/00, C 07 C 327/00, 317/00, 313/00
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸	

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document ¹¹ with indication, where appropriate, of the relevant passages ¹²	! Relevant to Claim No. ¹³
A	EP, A, 0236872 (F. HOFFMANN-LA ROCHE) 16 September 1987 see claim 1 cited in the application --	1-17
A	EP, A, 0012401 (MERCK & CO. INC.) 25 June 1980 see claim 1 cited in the application --	1-17
A	DE, A, 2720996 (E.R. SQUIBB & SONS) 24 November 1977 see claim 1 cited in the application & US, A, 4105789 --	1-17
A	EP, A, 0274453 (LABORATOIRE ROGER BELLON) 13 July 1988 see claim 1 --	1-17
A	EP, A, 0214639 (G.D. SEARLE) 18 March 1987 see claim 1 --	1-17
		./.

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

8th March 1990

Date of Mailing of this International Search Report

17 APR. 1990

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

T. TAZELAAR

III. DOCUMENTS CONSIDERED TO BE RELEVANT: (CONTINUED FROM THE SECOND SHEET)

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ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

GB 8901399
SA 33118

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/04/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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